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THE DIASTOLIC MURMUR OF MITRAL STENOSIS*

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BECAUSE of the great interest currently demonstrated in the surgical correction of mitral stenosis, it has become essential for the clinician to be able to diagnose this condition with the greatest possible accuracy and also to estimate the degree of disability caused by it. A thorough knowledge of the murmurs of mitral stenosis and of the variations in these murmurs under different physiologic and pathologic conditions should be of assistance in diagnosis. It is our purpose to present in this paper a brief history of the murmurs of mitral stenosis and various factors affecting these murmurs, as well as brief discussions of the opening snap and the third heart sound. We conclude with a summary of factors affecting the detection of the diastolic murmur of mitral stenosis and of factors in clinical examination that will aid in its detection.

DESCRIPTIVE HISTORY

A review of the descriptive history of the diastolic murmur of mitral stenosis indicates that during the past fifty years little has been added to knowledge of its cause and only minor points have been contributed to its clinical description.

Laënnec[1,2] gave impetus to auscultatory investigation by his invention of the stethoscope in 1819. For the next fifty years, French, German and English physicians recorded their impressions, which were frequently erroneous, to be sure, but contained surprisingly often the germ of what appears presently to have been the truth.

Foremost in the French assemblage were Gendrin,[3] Fauvel,[4] Beau,[5,6] Hérard,[7] Bouillaud,[8,9] Lemaire[10] and Racle.[11] The Germans were represented by Constatt,[12] Wintrich,[13] Friedrich,[14] Felix von Niemeyer[15] and Paul Niemeyer,[16] who patterned their investigations along similar lines. Concurrently, contributions from the British Isles were made by Hope,[17] Williams,[18] Markham,[19] Walshe[20] and Gairdner[21-23] and from America by Austin Flint.[24-33]

The English physician, James Hope,[17] in 1832, described the murmurs as follows:

> . . . murmurs are not, as is often supposed, louder, *caeteris paribus*, in proportion as the valvular contraction is greater. On the contrary, the loudest murmurs are produced by a moderate contraction, and they become weak when it is extreme . . . a contraction of the mitral or tricuspid valve to only two, three, or four lines [one line = *1/12* inch] in diameter, I have frequently known to occasion little or no murmur.

In 1841, Gendrin,[3] of the French group, first used the term presystolic. Two years later, Fauvel[4] was the first to demonstrate that the murmur of mitral stenosis was presystolic. Hérard,[7] who closely followed Fauvel in his writings, seems to have been well aware of the effects of atrial fibrillation and congestive heart failure on the murmurs of mitral stenosis.

The early German literature on the mitral diastolic murmur closely followed the patterns of the French. These writings were well reviewed in 1872 by Fagge.[34]

Much of the early British concern with cardiac murmurs was voiced by the writers mentioned above. Hope[17] early recognized that the intensity of an apical diastolic murmur did not necessarily indicate the degree of mitral stenosis. Williams[18] distinguished the diastolic murmur of mitral stenosis from that of aortic regurgitation, and Markham[19] described the loud apical first heart sound in some cases of mitral stenosis. Later, Gairdner,[21-23] of Scotland, introduced the concept that the presystolic part of the murmur of mitral stenosis was due to atrial systole.

Concurrently with the investigation of Gairdner[21-23] in Scotland, Austin Flint,[24-33] in the United States, was following a similar line of thought and was writing extensively on the presystolic murmur, but he paid little attention to the murmur occurring during mid-diastole.

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Various Factors Affecting the Murmurs

Effect of Change of Rhythm on the Presystolic Murmur

Fagge[34] was one of the first to note that the presystolic murmur could be altered by a change in rhythm. In his treatise he reported a case in which the heart was liable to sudden changes in rhythm, from regularity to a bigeminy, with probable dropping of every third beat and corresponding changes in the mid-diastolic and presystolic murmurs.

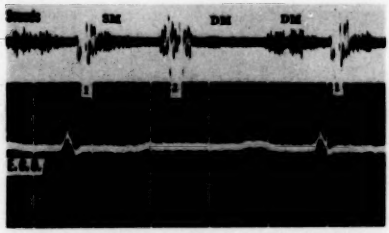


Figure 1. *Apical Tracings in M.B., a Forty-four-Year-Old Woman with a History of Rheumatic Heart Disease since Childhood and Considerable Limitation of Activity during the Last Few Years.*

The phonocardiogram shows the effect of a long PR interval on the atrial systolic murmur (DM), which becomes late diastolic rather than presystolic.

The first diastolic murmur (DM) is a rumbling, low-pitched, low-intensity murmur occurring around the time of the normal third heart sound.

The second diastolic murmur (DM) is equivalent to an atrial systolic murmur that follows the P wave of the electrocardiogram (E.C.G.) and is separated by a considerable interval from the first heart sound.

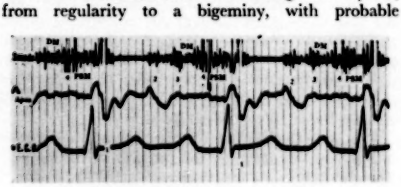


Figure 2. *Apical Tracings in M.A., a Twenty-two-Year-Old Man with Rheumatic Heart Disease and Mitral Stenosis.*

The phonocardiogram illustrates the fact that with intense atrial activity and a slightly prolonged PR interval (0.26 second), a presystolic gallop (4) may be present together with a presystolic murmur (PSM), which is thus not crescendo in type. If the PR interval had been normal, the murmur would doubtless have been a presystolic crescendo.

The earlier part of the diastolic murmur (DM) becomes evident at the time of the third heart sound (rapid ventricular filling) although it starts before it at the opening of the mitral valve.

Effect of First-Degree Heart Block on the Presystolic Murmur

Galabin,[35] using a modification of Marey's cardiograph, found, in 1875, that in certain cases the diastolic murmur began shortly after the second sound and was separated by a short pause from the first sound (Fig. 1-3).

Effect of Second-Degree and Third-Degree Heart Block on the Diastolic Murmur

Many years after Galabin,[35] Sir Thomas Lewis[36,37] pointed out the effect of atrial systole on the mitral diastolic murmur in cases of heart block, noting that a murmur occurred with each atrial contraction (Fig. 4).

Effect of Atrial Fibrillation on the Presystolic Murmur

There is no doubt that a murmur can be heard in presystole in cases of mitral stenosis with atrial fibrillation when diastole is short. This murmur is not the atrial systolic murmur described by Gairdner[21-23] but is due simply to the falling of the first heart sound earlier than usual in diastole because of the rapid heart rate. If the rate slows, or if there is a long diastolic pause, the diastolic murmur will be found to fade off in a decrescendo fashion (Fig. 5 and 6).

The best description of this phenomenon occurs in Sir James MacKenzie's[37] detailed discussion of the subject in 1913.

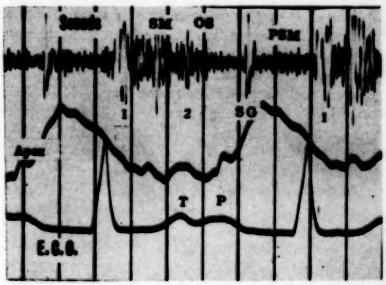


Figure 3. *Apical Tracings in D.M., a Nineteen-Year-Old Girl with Active Rheumatic Fever (Third Attack), Mitral Regurgitation, Mitral Stenosis, Aortic Regurgitation and First-Degree Heart Block.*

The phonocardiogram illustrates another effect of a long PR interval on the cardiac sounds. The first heart sound is moderately intense despite the long PR interval of 0.29 second. The second sound is of rather low intensity at the apex, and an opening snap (OS) of the mitral valve, consisting of several moderately high-frequency vibrations, is seen. The third heart sound is unusually prominent and is considerably louder at the apex than the second heart sound, which is to some extent obscured by the systolic murmur (SM). The atrial sound may be summated with the third heart sound and is also concerned with the murmur (PSM) that fills the interval between the third and first sounds but without presystolic crescendo. The systolic murmur is crescendo-decrescendo and fills systole. The summation gallop (SG) results from an accentuation of the normal third heart sound as a result of relatively early atrial contraction secondary to the prolonged PR interval.

Effect of Ventricular Premature Beats on the Presystolic Murmur

It is obvious that no atrial systolic murmur will be heard before the first heart sound of a ventricular premature beat, since there is no preceding atrial contraction. It is interesting that the presystolic murmur

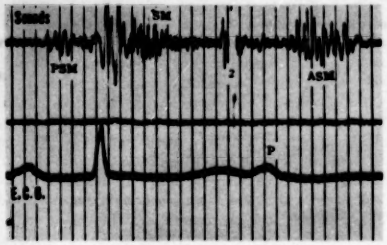


FIGURE 4. *Apical Tracings in N.M., a Sixty-five-Year-Old Woman with a Long History of Hypertension and Complete Heart Block.*

There was no definite history of rheumatic fever. The phonocardiogram demonstrates the fact that atrial systole is capable of causing a loud atrial systolic murmur (PSM) and (ASM) and that its position in diastole varies with the position of the P wave of the electrocardiogram.

resulting from atrial contraction may also be absent in the beat that follows the ventricular premature beat. A possible explanation for this is the fact that, owing to the long compensatory pause, the left ventricle may become filled with blood so that the atrium cannot push enough extra blood through the mitral orifice in late diastole to create a murmur (Fig. 7).

Effect of the Valsalva Maneuver on the Diastolic Murmur of Mitral Stenosis

It has been shown that the mitral diastolic murmur can be affected in many different ways, depending on variations in cardiac rhythm. It is also possible to alter the murmur considerably by such a simple maneuver as forced expiration against a closed glottis (Valsalva's maneuver). The positive pressure that develops within the thorax decreases venous return and in turn decreases flow through the mitral-valve orifice. The enlarged left atrium continues to beat forcibly, and a presystolic murmur may be converted into an atrial sound, giving a presystolic gallop (Fig. 8*A* and *B*).

Effect of Exercise and Change of Position on the Diastolic Murmur of Mitral Stenosis

Friedrich[14] stated in 1867 that a dull or reduplicated diastolic tone could frequently be converted into a distinct diastolic murmur when a patient was made to walk up and down to accelerate the heart's action.

FIGURE 6. *Apical Tracings in L.S., a Thirty-two-Year-Old Woman with Rheumatic Heart Disease, Mitral Stenosis, Mitral Regurgitation, Aortic Regurgitation (Slight) and Atrial Fibrillation.*

The phonocardiogram demonstrates the great variability in the diastolic murmur in relation to cycle length. In the first and third cycles the murmur runs throughout diastole and is of moderate intensity. In the second cycle the third sound is followed so rapidly by the first sound of the next cycle that a crescendo effect results on auscultation.

Bramwell,[38] in 1881, further observed that "in some cases of mitral stenosis the murmur disappears when the position of the patient is altered, when he gets up, but the rhythm of the murmur does not change; it always remains presystolic." The subject of the effect of change in position (Fig. 9) was more fully studied by Gowers.[39]

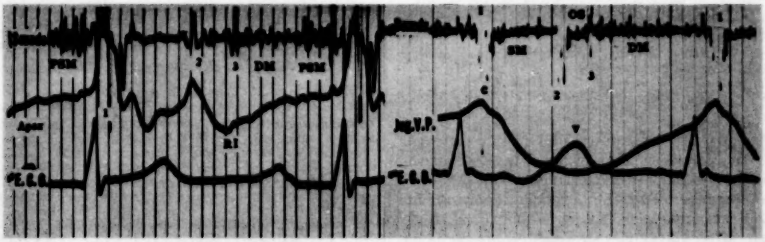


FIGURE 5. *Apical Tracings in M.A., a Thirty-two-Year-Old Man.*

The phonocardiogram (A) *demonstrates a presystolic crescendo murmur (PSM) when normal rhythm is present. (RI = rapid inflow).* B *shows phonocardiogram in the same patient after the onset of atrial fibrillation. Note that the diastolic murmur still extends into presystole but that there is no crescendo effect.*

Effect of Mitral-Valve Surgery on the Diastolic Murmur of Mitral Stenosis

Mitral-valve surgery may have no effect whatso-

ever or may affect the diastolic murmur of mitral stenosis in many ways. If there is a very slight murmur before operation, because of tight mitral stenosis, this murmur may greatly increase after operation because of the increased blood flow over the roughened and torn valve margins. Moreover, a murmur of moderate to loud intensity may be decreased after operation if the split is relatively smooth and no increased vibration results. In some cases the murmur is relatively quiet for a few weeks to a few months after operation and then seems to increase in intensity, perhaps owing to the development of further stenosis. In some patients who have been fibrillating before operation a return to normal sinus rhythm after operation may be accompanied by the return of a presystolic crescendo murmur. Conversely, in patients who have normal sinus rhythm and who fibrillate in the first few days or weeks after operation the atrial systolic murmur will disappear. The development of other bizarre rhythms will, of course, alter the murmur in various ways. It is thus seen that the effects of mitral-valve surgery on the diastolic murmur may vary greatly, as one would expect (Fig. 10*A* and *B*).

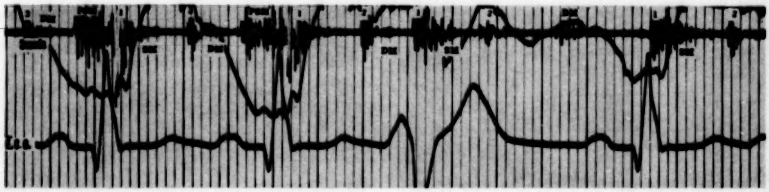


FIGURE 7. *Apical Tracing Illustrating the Absence of the Presystolic Murmur in the Ventricular Ectopic Beat and Also after the Compensatory Pause.*

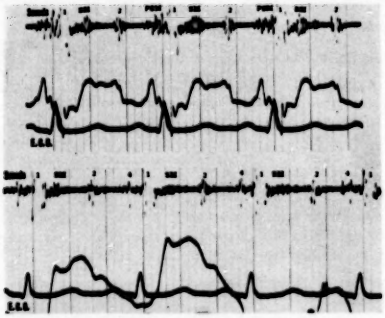


FIGURE 8. *Apical Tracing, Showing Presystolic Murmur (PSM) before the Valsalva Maneuver* (A) *and* (B) *Alteration of the Presystolic Murmur to an Atrial Sound (4), Giving a Presystolic Gallop Secondary to the Valsalva Maneuver.*

Disappearance of the Presystolic Murmur during Congestive Heart Failure

Although in 1854 Hérard[7] had described the fact that the diastolic murmur of mitral stenosis sometimes disappears during congestive heart failure, it was not until 1901 that Broadbent[40] called attention to the disappearance of the presystolic murmur in failure and presented possible causes for this, the most probable one being the establishment of tricuspid incompetence. The giving way of the tricuspid valve and the occurrence of considerable reflux into the right atrium make it impossible for the right ventricle to sustain the high pressure in the pulmonary circulation and the left atrium that was present previously.

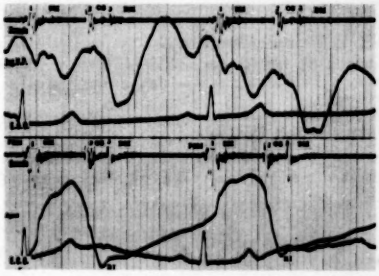


FIGURE 9. *Apical Tracings, Showing the Effect of Exercise on the Diastolic Events in a Case of Mild Mitral Stenosis. In the upper tracing the second sound can be seen followed by an opening snap and then by a third heart sound and a short diastolic murmur, which, owing to the slow heart rate, is early diastolic rather than mid-diastolic. A slight presystolic murmur is also present. After exercise (lower tracing) the only significant alteration is in the greatly increased intensity of the third heart sound. For some reason the opening snap has lessened in intensity and would doubtless be inaudible. The presystolic murmur has altered very little.*

There is not, therefore, sufficient pressure to force the blood through the mitral orifice rapidly enough to generate a murmur.

Despite the many brilliant clinical observations concerning the presystolic murmur, the theory of its causation and indeed of its actual existence was by no means universally accepted.

Ormerod,[41] in 1864, disputed the atrial systolic origin of the murmur described by Gairdner[21] on the grounds that the atrial contraction was too weak and brief to cause so loud a sound, which he held to be due rather to the contraction of the ventricle and to be regurgitant.

Barclay,[42] eight years later, maintained that the so-called presystolic murmur was really systolic and that although indicative of a contracted mitral orifice, it was regurgitant. He called attention to the absence of valves in connection with the pulmonary veins, pointed out that with no means of closing the outlet backwards, the atrium could expand but had little power to drive the blood forwards, and claimed that it "was scarcely possible that one of the loudest and roughest murmurs ever heard in cardiac disease should be produced by contraction of the auricle."

The suggestion has been made that the presystolic murmur heard in cases of mitral stenosis with atrial fibrillation is really a systolic murmur and is due to the combined effect of mitral regurgitation occurring very early in systole and followed by a delayed first sound.

Opening Snap of the Mitral Valve

The opening snap of the mitral valve may be heard in many cases of mitral stenosis. It is due simply to a delay and an accentuation of the normal fourth component of the second heart sound—that is, the opening of the atrioventricular valves. It was first described by Duroziez[43,44] in 1862, when he introduced his onomatopoeia, "ffouttatarou." The "ffout" corresponds to the crescendo presystolic murmur and ends abruptly in a snapping first heart sound; the "tata" refers to the second heart sound closely followed by the opening snap of the mitral valve, and the "rou" to the low-pitched diastolic rumble. The actual term "opening snap," or its French equivalent, was introduced by Rouches[45] in 1888 as "claquement d'ouverture de la mitrale."

A third sound coming close after the second sound may be difficult to differentiate clinically from the opening snap, but usually the opening snap, being of higher frequency than the third sound, has a high-pitched, dry quality, whereas the third sound is dull and low pitched.

Another difficulty occasionally encountered is the differentiation of an opening snap from a split second sound. There is a very short interval between the two components of a split second sound, and the components are usually of similar intensity to the ear. No reliance can be put on the fact that a split second sound is said to be heard best at the base and an opening snap at the apex. Margolies and Wolferth,[46] in 1932, pointed out that the opening snap is often best heard at the base, and we have also recorded this fact on a number of occasions.

The phonocardiogram often helps differentiate a split second sound, a second sound combined with opening snap, and a second sound together with a third heart sound or any combination of these three sounds. If a good tracing of an apex cardiogram can be obtained simultaneously with the sound tracing, differentiation is easy. However, a good apex cardiogram is not always obtainable, and time intervals may then be of some assistance.

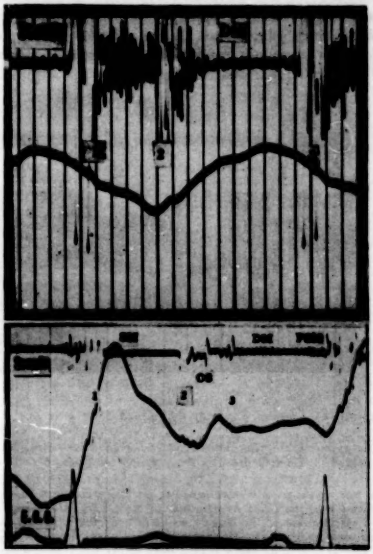


Figure 10. *Apical Tracings in D.H., a Thirty-seven-Year-Old Woman with Rheumatic Heart Disease, Mitral Stenosis and Atrial Fibrillation.*

Before operation in 1951 (A) *the patient had a very loud systolic murmur just medial to the apex, and the apical diastolic murmur could not be identified with any degree of certainty. It was thought that the systolic murmur might have been due to tricuspid incompetence* (B). *Two years after operation the systolic murmur of tricuspid regurgitation has disappeared. The rhythm has reverted to normal; an opening snap, third heart sound, diastolic murmur and presystolic with slight crescendo are now easily identified. (This patient was converted from a cardiac cripple before operation to a relatively normal, active, healthy woman.)*

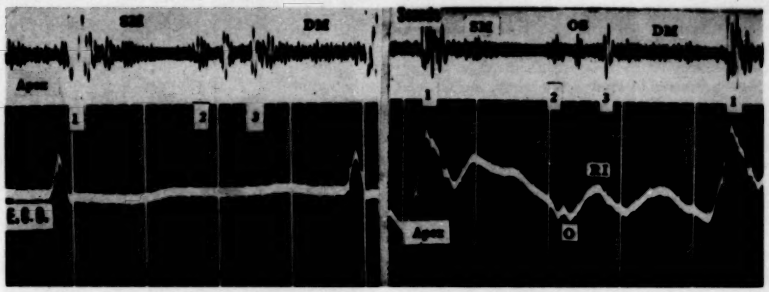
In relation to the apex cardiogram, the split second sound has its second component before the 0 point (opening of the atrioventricular valves). An opening snap is synchronous with the 0 point, and a third sound occurs at the summit of the rapid inflow wave (Fig. 11*A* and *B*).

So far as time intervals are concerned, the duration between the two components of a split second heart sound is usually less than 0.07 second. The interval between the beginning of the second sound and the opening snap is at least 0.08 second, and that be-

tween the beginning of the second-sound complex and the third sound is about 0.12 second.

It is important to realize that the opening snap is one of the few signs in mitral stenosis that may persist even when the murmurs become equivocal or absent, as during atrial fibrillation or failure, or both.

In 1951 Messer et al.[47] studied the interval between the onset of the valvular component of the second heart sound and the opening snap in cases of atrial fibrillation. They found that this interval depended largely on the duration of the preceding RR interval. They also noted that the opening snap sometimes appeared closer than 0.07 second to the valvular elements of the second heart sound, emphasizing the importance of relating the duplicated second sound to the apex cardiogram for accurate interpretation of the nature of this reduplication.



A B

FIGURE 11. *Apical Tracings in F.O., a Sixty-nine-Year-Old Woman with Atrial Fibrillation, Minimal Aortic Regurgitation, Mitral Regurgitation and Mitral Stenosis.*

The phonocardiogram demonstrates the need for taking an apex cardiogram to be sure whether three sounds following close together in diastole are due to a split second sound combined with an opening snap or a second sound combined with an opening snap and a third sound.

In tracing A, *with a simultaneous electrocardiogram, it is not possible to be certain of the origin of the sound between the second and the third heart sounds. However, in the lower tracing the apex cardiogram makes identification easy, showing the middle one of the three sounds to coincide with the valley or "O" point of the apex cardiogram. This is the opening of the atrioventricular valves and the beginning of the rapid inflow wave; hence, the intermediate sound is an opening snap. The third sound falls at the apex of the rapid inflow wave and so is a true third heart sound.*

First Heart Sound in Mitral Stenosis

Accentuation of the first heart sound, giving it a loud, snapping quality at the apex, is another important and fairly common sign in mitral-valve disease. It is sometimes the first suggestion of fibrosis and early stenosis but may, of course, result from other conditions, such as exercise, thyrotoxicosis, neurocirculatory asthenia and nodal rhythm. There are many cases of long-standing mitral stenosis, however, in which the first heart sound is of low intensity or is masked by a systolic murmur that follows immediately. Accentuation of the first sound is more significant of mitral stenosis when found in association with other signs, such as an enlarged left atrium or an accentuated pulmonic second sound.

Even when the first sound is not increased in intensity it may be abnormal by phonocardiogram. This is shown by a delay of the maximum vibrations of the first heart sound in relation to the QRS complex of the electrocardiogram. This was described by Cossio and Berconsky[48] in 1943 and again by Wells[49] in 1952. Wells considered the delay to be more significant than abnormality of frequency or intensity of the first heart sound. However, in many cases of mitral stenosis, no delay can be detected. Wells[49] states that the main components of the first heart sound should occur within 0.06 second of the onset of the QRS complex and that, if they occur at 0.07 second or later, it should be classified as "late."

Third Heart Sound in Mitral Stenosis

It has been stressed that all possible aid is required to estimate the degree of disability caused by mitral stenosis. In this regard the presence or absence of a third heart sound may be of some assistance. Since it is generally accepted that the third heart sound results from the rapid inflow of blood from the left atrium to the left ventricle early in diastole, it is not unreasonable to suppose that as blood flow becomes diminished secondary to tight mitral stenosis the third heart sound progressively lessens in intensity and finally disappears. In our limited number of cases, we have found this to be true. We have also observed the converse — namely, that some patients with typical murmurs of mitral stenosis and good tonus of the left ventricle but with a prominent third heart sound have not been unduly incapacitated by

their mitral stenosis, supporting the concept that a loud, apical, third heart sound means good filling of the left ventricle. As pointed out by Hope[17] over a hundred years ago, the moderate cases of mitral stenosis often had the loudest murmur, and this may be misleading clinically since a loud mitral diastolic murmur frequently suggests to the physician or surgeon that the degree of stenosis is marked. It is suggested that the presence of a loud third heart sound at the left ventricle in the presence of the diastolic murmur of mitral stenosis indicates that the degree of stenosis is not unduly severe (Fig. 11*A* and *B*).

Factors Affecting the Detection of the Diastolic Murmur

If a loud systolic murmur is present at the apex or if a loud opening snap or loud second heart sound is heard in the same region, the diastolic murmur may be missed because of fatigue and masking effects on the human hearing mechanism. This is especially so in cases in which the diastolic rumble is low pitched or of short duration.

The murmur may be missed in the presence of tachycardia, either with regular rhythm or in the presence of atrial fibrillation or flutter.

Even though mitral stenosis may be considered to be present clinically this does not mean that the hemodynamics are identical in all cases. The valve mechanism, the size of the mitral orifice, the direction of blood flow from atrium to ventricle, the point whether the valve orifice is centrally or eccentrically placed, and the question whether the valves are moderately or greatly thickened or calcified may all be involved in varying the nature and intensity of the diastolic murmur of mitral stenosis.

Especially in patients in the older age group, the presence or absence of heart failure may cause one to miss or detect the murmur. This is particularly true in patients with a very tight stenosis.

A word of warning is necessary in the assessment of mitral stenosis based on the intensity of the apical diastolic murmur with or without presystolic crescendo. Hope[17] pointed out that moderate stenosis gives the loudest murmur and that tight mitral stenosis may exist with little or no murmur. Hérard[7] observed that in patients in failure or with rapid irregular rhythm the murmur may be absent. Other authors have emphasized the fact that many conditions other than mitral stenosis may be accompanied by an apical diastolic murmur.

We have repeatedly observed patients in the older age group with a long history of rheumatic heart disease and the clear-cut murmurs of mitral stenosis who suffer very little disability and who can do a full day's work. These patients, who often survive to a ripe old age and live full and useful lives (Fig. 11*A* and *B*), should not be subjected to surgery, which carries a definite risk at any age and a greater risk in the later decades. On the other hand, patients in failure, even without a murmur, who have an enlarged left atrium, right-axis deviation by electrocardiogram and a history of hemoptysis and perhaps even of rheumatic fever, should be very fully investigated to rule out the possibility of mitral stenosis. A loud apical first sound or the finding of an opening snap, possibly in the presence of an accentuated pulmonic sound, may be all the auscultatory evidence available to make the diagnosis in these cases.

Factors in Clinical Examination Helping Detect the Diastolic Murmur

It is essential that the physician carry out his auscultation under ideally quiet conditions.

The patient should hold his breath comfortably in moderate expiration.

As Levine and Harvey[80] have emphasized, the physician must acquire the habit of listening specifically to the individual events of the cardiac cycle. He must concentrate on the first sound to the exclusion of all else, then on the second sound, then on systole and finally on diastole. There is no other way of accurately timing murmurs and heart sounds or even of being certain of the existence of the lower-pitched murmurs and sounds.

In listening for the low-frequency mid-diastolic rumble of mitral stenosis, the bell of the stethoscope is generally more useful than the diaphragm, which tends to screen out the lower-frequency sounds so that it may enable those of higher frequency to be heard more easily.

When the bell is used, one should apply it first of all firmly to the chest wall and, while listening intently, gradually relax the pressure of the bell against the skin. A murmur at first inaudible with firm pressure may become clearly audible with light pressure. The reason for this is that firm pressure of the bell against the chest causes the skin to be stretched tightly across the mouth of the bell so that a high-frequency diaphragm is created. Relaxing this pressure converts the bell to a low-frequency recorder, and so the murmur may be heard.

Exercising the patient and turning him on his left side, a maneuver known to all physicians but not always employed, should be done in every case.

Careful searching in the area of the apex is essential, since, although some murmurs may be heard over a reasonably large area, others are often restricted to small areas of 2.5 to 5 cm. in diameter. Hence, careful and diligent listening is required in any suspected case if errors are to be avoided.

The murmur in some cases may vary, depending on such factors as heart rate, the presence or absence of atrial fibrillation and congestive heart failure and the natural progression of the disease. The murmur may thus be heard by an observer one day and not

by the same observer on the next day or even six months or a year or more later. Conversely, a patient entering the hospital in failure may have no detectable murmur, and yet, when the rate and rhythm are controlled by digitalis and by bed rest and the failure benefited by drugs, a salt-free diet and mercurial diuretics, a mid-diastolic murmur, possibly with presystolic crescendo, may become clearly audible. These changes, which may occur with varying degrees of valve damage, depend on the relation between the shape of the valve orifice and the rate of blood flow through the orifice and on whether or not turbulence results in the blood stream.

If a patient is admitted to the hospital with failure or a condition resembling cor pulmonale and no mitral diastolic murmur is heard, and if the record shows that some previous observer heard a murmur of mitral stenosis, one should not be too hasty in deciding that the earlier observer was in error. It is not impossible that as the stenosis has increased the murmur has lessened until finally it has become inaudible. We have frequently encountered this situation. In such cases, if the first sound seems too "good,"—that is, louder than appears consistent with the degree of myocardial failure,—mitral stenosis should be suspected. This is especially true if atrial fibrillation and hypertrophy of the right ventricle are present.

The presystolic crescendo of the mitral diastolic rumble is not present in all cases of mitral stenosis. This fact was pointed out by Sansom,[51-56] Johnston[57] and Battro and Braun-Menéndez.[58] Sometimes, the mid-diastolic murmur is recorded as diminuendo and may in fact almost disappear just before the first heart sound. This occurs especially during the long diastole in patients with a slow heart rate or when the atrial contraction is feeble or absent.

On the other hand, cases are often reported in which a presystolic crescendo murmur has been heard on auscultation but no abnormality of the mitral valve is detected at autopsy. Alimurung, Rappaport and Sprague[59] reviewed the causes for this phenomenon in 1949.

In any case in which an opening snap is heard, it is well to suspect mitral stenosis, even if no diastolic murmur is heard and especially if the condition clinically resembles mitral stenosis.

When a loud snapping first sound is heard at the apex with no obvious cause, such as thyrotoxicosis or neurocirculatory asthenia or nodal rhythm, one should search carefully for a mid-diastolic or presystolic murmur. However, a quiet or normal first sound at the apex does not exclude the possibility of mitral stenosis.

Conclusions

The diagnosis of mitral stenosis may be very easy or extremely difficult, and all possible information is desirable in the evaluation of each case. A good clinical history, physical examination, electrocardiogram and x-ray fluoroscopy are all essential. Often auxiliary aids, such as a jugular-pulse tracing, help differentiate mitral regurgitation from tricuspid insufficiency in cases in which a systolic murmur is heard just medial to the apex.

Even with the greatest of care in diagnosis in the best of clinics, errors are not infrequent. Some patients with clinical diagnoses of mitral stenosis have been found at operation to have free mitral regurgitation and no stenosis. Some cases diagnosed as cor pulmonale have been found at autopsy to be tight mitral stenosis, and others diagnosed as severe mitral regurgitation with slight mitral stenosis have turned out to be cases of tricuspid regurgitation with tight mitral stenosis.

These errors are occurring in clinics where excellent clinicians are working under ideal conditions. It is therefore essential that every physician examine his patients with the utmost care.

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PELGER–HUËT ANOMALY OF THE LEUKOCYTES*

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IN 1928, Pelger,[1] a Dutch physician and specialist in tuberculosis, examined the blood smear of a tuberculous patient and noted the absence of the usual nuclear segmentation in the granulocytic leukocytes. A large percentage of the cells were stab forms. The rest showed only two segments, and a few showed three segments but none more than three. In spite of this apparent immaturity, the nuclear chromatin was coarse, grouped into irregular clumps and obviously quite mature. In 1931, he had another case, again in a patient with tuberculosis, and thus the condition was first associated with this disease.[2] Later in the same year, a Dutch pediatrician named Huët[3] examined a ten-year-old girl suspected of having tuberculosis. He found the Pelger anomaly but no tuberculosis; on carefully taking the family history, he discovered that the girl was a niece of one of Pelger's patients. He then demonstrated the familial and hereditary nature of the condition and suggested that it was inherited as a nonsex-linked mendelian-dominant characteristic. He traced this family tree back three generations and found elders possessing the anomaly who were in good health. Huët concluded that no pathologic implications could be attributed to the condition. Schilling subsequently proposed that the condition be called the Pelger–Huët anomaly. It has also been called by the descriptive term, "familial false shift to the left of the leukocytes."

Since 1932, when Huët[4,5] described 2 more families from Holland with this anomaly, many additional cases have been discovered and reported. By 1940, 210 patients in 32 families had been described.[6] Most of these reports appeared in the European literature, and a few in other parts of the world, such as Japan, Java, the West Indies, Israel and Australia.[7-55]

Interestingly enough, as far as we know, no report has emanated from Great Britain, and only 2 cases have been described in the United States. Peterson[34] reported the anomaly in a Chinese family in 1935, and Tileston[45] presented a case in 1937.

The actual number of cases certainly exceeds that reported in the medical literature. Probably, they are not as rare in the United States as the scarcity of reports suggests.

Since recognition of this hematologic anomaly has practical significance and very little on the subject has been written in English, it was considered timely to review the problem in connection with a recently encountered case. It is of additional interest that the

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anomaly was unresponsive to cortisone administration and that to our knowledge, this is the first case with an autopsy report.

Case Report

A 46-year-old man was admitted to the Neurological Service on February 10, 1954. Only a brief summary of his illness, which had no connection with his Pelger–Huët blood anomaly, is presented here. He had been well until early 1953, when he became less talkative and showed recent

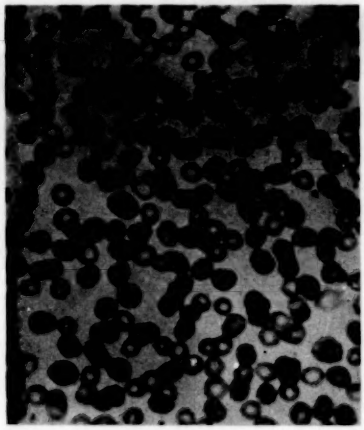

FIGURE 1. *Photomicrograph (Low Power) of the Blood Smear.*

memory loss, apathy, indecision, difficulty in concentrating, and confusion. In January, 1954, a brain biopsy was performed, and histologic examination revealed neuronal degeneration. The patient was transferred to the Veterans Administration Hospital for continued care. His course was gradually downhill, complicated by repeated episodes of aspiration pneumonia due to increasing weakness of the swallowing mechanism. He presented a serious feeding problem, and, in spite of all efforts, his nutritional status gradually deteriorated. He finally died on October 7.

The past history revealed that he had been an active normal child. In 1926 he had had pneumonia and an appendectomy. He had had a slowly progressive visual difficulty, since the age of 8, corrected with glasses.

On the paternal side, the grandfather had died of heart disease. The cause of the grandmother's death was unknown. An uncle had died at 31 of heart disease. On the maternal side, the grandparents had died of unknown causes. An uncle had died at 65 of heart disease. The mother was living and well at the age of 73, with no known history of any hematologic disorder. The patient had 2 sisters living and well, aged 43 and 38. The younger sister had had a "nervous breakdown" at the age of 11. The older sister had been under medical care for a "blood condition" for many years. The patient's wife was in good health. They had 2 sons, aged 6 and 11, and 1 daughter, aged 9; all were well, although the daughter had a history of asthma and other allergy.

While the patient was on the Neurological Service, a routine blood smear was reported as showing a marked granulocytic shift to the left. Because there was no apparent explanation for this laboratory finding, the patient was transferred to the Medical Service for further investigation. A study of the granulocytic series of the leukocytes revealed the following deviations from normal: the nuclear-cytoplasmic ratio was noted to be smaller than normal. The number of stab forms was greatly increased. Hardly any polymorphic nuclei with more than 2 segments were seen; the nuclei were of peanut, pince-nez or dumb-bell shape. All granulocytic nuclei were coarse, mature, and pitted with condensed masses of chromatin (Fig. 1 and 2). It was obvious that we were dealing with Pelger–Huët anomaly of the granulocytes.

Investigation of other members of the patient's family disclosed the presence of this anomaly in both sisters, 1 nephew and 1 of the patient's 3 children (Fig. 3).

The repeated white-cell counts are recorded in Table 1. The normal total count was associated with a high percentage of stab cells. The patient had 1 of his aspiration-pneumonitis episodes on April 28, with leukocytosis and an increased granulocytic shift to the left. In view of the known effect of cortisone on hematopoiesis, we were curious to learn if this hormone would correct the Pelger–Huët anomaly. Cortisone was administered by intramuscular injection in the amount of 300 mg. on September 7, 200 mg. on the following day, and 100 mg. daily during the next 5 days, through September 13. As a known response to cortisone, the total white-cell count promptly rose to 28,500, with an increase in the granulocytic shift to the left. The Pelger–Huët anomaly, however, remained unchanged.

Sternal-bone-marrow aspiration was attempted on 2 occasions, but no marrow could be obtained. This difficulty

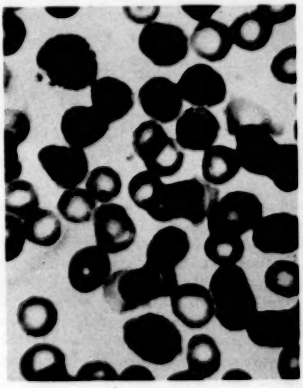

FIGURE 2. *Photomicrograph (High Power) of the Blood Smear.*

was later explained by the post-mortem examination of the bone marrow. On September 24, an iliac-crest bone biopsy was performed. Histologic examination of this specimen revealed that the bone cancelli were delicate and widely spaced. Most of the marrow space was taken up by a pale, eosin-staining, homogeneous material consisting of degenerated fat tissue characteristic of inanition. Narrow strands of cellular bone marrow demonstrated megakaryocytes and red-cell elements in the usual fashion. The granulocytic series showed a relative increase in myelocytes; the maturing forms disclosed the typical dumb-bell and pince-nez forms of the Pelger–Huët anomaly. There was also a slight eosinophilia, the eosinophilic granulocytes having nuclei identical with those of the neutrophils.

At autopsy the body gave evidence of severe inanition. The heart was small, weighing 230 gm. The right atrium and right ventricle were dilated. Remnants of subepicardial fat tissue were gelatinous in appearance. The bronchi contained purulent exudate. Multiple foci of aspiration pneumonitis

in the lower lobes of both lungs were partly of recent origin; others were in various stages of organization. The spleen was small, weighing 50 gm. The follicles were atrophic; other pertinent gross or microscopical findings were present only in the central nervous system and in the bone marrow.

The brain showed grossly a moderate cortical atrophy. Microscopically, in cortex, striatum and thalamus, the nerve

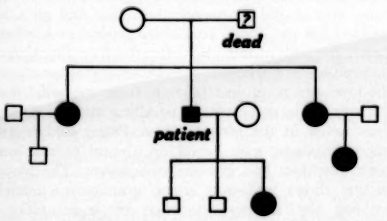

FIGURE 3. *Pedigree of a Patient with Pelger-Huët Anomaly. The circles denote female, and the squares male members of the family. Blacked-in squares and circles indicate the presence of the anomaly.*

cells indicated diffuse degenerative changes; there was loss of cells and astroglial reaction. The orbital regions were most severely affected. The neuropathological diagnosis was presenile dementia of the Jakob type (corticostriospinal degeneration).

The bone marrow of the vertebras, ribs and pelvis was pale red. Microscopically, it consisted largely of atrophic fat tissue, as it appears in states of severe inanition: an almost homogeneous, pale, eosin-staining material, between which there were narrow strands of cellular bone marrow. The composition was within normal limits, except for a slight relative increase in eosinophils. Megakaryocytes were few in number; those present were in various stages of maturation. The striking deviation from the norm was the absence of multilobulated granulocytes. Both eosinophilic and neutrophilic ripe forms of granulocytes had stab or dumb-bell shaped nuclei, as also seen in the peripheral blood.

DISCUSSION

Whereas the normal blood smear shows nonsegmented nuclei in about 3 to 5 per cent of the neutrophils, 2 segments in 15 to 20 per cent, 3 or 4 segments in 70 to 75 per cent and more than 4 segments in about 5 per cent, in the Pelger-Huët anomaly there is an arrest of segmentation at the 2-lobe level. Therefore, one sees an increased number of stab or younger neutrophils; the rest show 2 segments with only a rare cell containing 3 segmented nuclei. The nucleus has a dumb-bell, peanut, or pince-nez appearance. Maturation of the cell proceeds without the normal segmentation. The chromatin network shows an intense staining reaction with basic dyes, appearing very coherent, with molded clumps and chromatin dots that are often in the blunt ends of the nuclei. Vacuoles are sometimes seen, and pyknosis of the chromatin may be present. In general, the Pelger nucleus is smaller than a normal nucleus in relation to the cell. The eosinophils are altered in the same fashion as the neutrophils, though the diminished segmentation of nuclei is not conspicuous in the eosinophils since about 75 per cent of the normal eosinophils have 2 lobes and only about 25 per cent have more than 2. The basophils are similarly involved, but because of their small number and usual low segment count, even in normal smears, the anomaly is not readily seen in the basophilic cells.

Bone-marrow examination shows an increase in myelocytes, metamyelocytes and band forms and a lack of highly segmented granulocytes. The cell nuclei of the myelocytes are dark and coarsely pitted, instead of the more typical, lighter color of the younger cells. Similarly, the chromatin tends to clump

TABLE 1. *Total and Differential White-Cell Counts during the Hospital Course.*

DATE	WHITE-CELL COUNT	METAMYELOCYTES	STAB FORMS	SEGMENTED NEUTROPHILS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASOPHILS	REMARKS
		%	%	%	%	%	%		
2/23/54	5600	0	20	33	40	7	0	0	All segmented cells had only 2 segmented nuclei
3/ 9/54	5300	1	28	40	26	4	1*	0	
4/ 7/54	5800	1	18	28	42	7	3†	1	
4/28/54	12,000	7	65	13	9	0	0	0	Pneumonitis
5/ 4/54	9000	2	42	34	17	5	0	0	
7/28/54	6000	1	31	24	40	3	0	1	
9/ 8/54	13,400	2	50	40	7	1	0	0	Cortisone started on 9/7
9/ 9/54	28,500	1	62	25	10	2	0	0	
9/10/54	24,800	2	74	14	8	2	0	0	
9/13/54	23,400	2	85	7	6	0	0	0	Last cortisone injection
9/16/54	17,700	1	58	29	10	2	0	0	
9/17/54	9800	0	56	24	19	1	0	0	
9/20/54	10,700	1	48	17	32	2	0	0	
9/21/54	10,000	3	45	18	30	4	0	0	

*Band forms.
†1% metamyelocyte; 2% band forms.

in the center of the nucleus, which is frequently at the outer periphery of the cell, and the nucleus is relatively small in comparison to the cytoplasm.[56-59]

The Pelger–Huët blood anomaly has been demonstrated to be a hereditary nonsex-linked simple mendelian-dominant characteristic; its penetrance is thought to be almost 100 per cent.[6,60-62] Pelger cells occur normally and abnormally in various animals, such as rabbits, fowl, alligators, turtles and snakes, and some invertebrates, as described by Undritz, Schmidt and Knoll.[63-66] About the underlying mechanism of the hereditary anomaly, nothing is known. Undritz[48] postulated that physical and chemical factors produce an abnormal colloidal dispersion of the chromatin material and that this results in the coherent nuclear material, which resists segmentation. Stahel[67] thought that a predisposition to a specific type of bone-marrow reaction was inherited. Others have considered both exogenous and endogenous toxins as possible causes.

Nachtsheim,[6] who found 16 cases in 16,316 routine blood smears, estimated the incidence of Pelger anomaly in human beings at about 1:1000, equally distributed between males and females. Climate and racial background are of no significance.

From the standpoint of pathologic physiology, the Pelger–Huët anomaly is apparently a completely harmless condition — a mere morphologic deviation, comparable to ovalocytosis. Persons with the anomaly have been found in good health at all ages, and their longevity was not influenced by the anomaly. The question whether or not they have a deficient defense mechanism against infection has been investigated. Leitner and Gugelot[68] studied the phagocytic activity of these neutrophils; they found that mature Pelger cells have essentially the same functional capacity as normal mature white cells have, but that immature Pelger neutrophils have less phagocytic activity. They suggested that in severe infection, when the peripheral blood contains many immature Pelger cells, the patient's defense mechanism is less satisfactory than that of a normal person, and he may have less than average resistance to infection. Stahel[67] also believed that these patients have a deficient immune mechanism. However, analysis of the cases failed to prove an increased incidence of infections or any other illnesses. The patient described above experienced relatively good health until the onset of his neurologic problem.

All the foregoing observations and conclusions concern heterozygous persons, who inherited the Pelger gene from only one parent. The homozygous state — with Pelger genes inherited from both parents — was investigated in rabbits by Nachtsheim.[6] He mated heterozygous Pelger rabbits and found that in double dose (homozygote state) the Pelger gene had a lethal effect. Most of the homozygous rabbits died as fetuses. Of the 39 homozygous Pelger rabbits born, 27 died during parturition or shortly thereafter, and of the 12 that lived, only 2 survived for more than a few months — only 1 male and 1 female could be reared to maturity. Nachtsheim pointed out that these "super-Pelger" animals can be recognized at birth by their appearance and weight. They lag behind normal rabbits in development, and this difference increases after birth. Their limbs are disfigured, and the long bones curved and shortened; the radius and ulna, as well as tibia and fibula, are twisted around each other. Later, the radius and ulna often become fused, and the epiphyses thickened. These abnormalities cause the forelimbs to project laterally from the body, and the animals to move with a paddling motion. Other signs noted in the growing super-Pelger rabbits are microphthalmia, scab formation around muzzle and nose, salivation and extreme emaciation. The blood picture shows uniformly round granulocytic nuclei, without the slightest evidence of segmentation.[6] Klein[69] studied the six animals histologically and found hyperplasia of the diaphyses and chondrodystrophy. The ribs were affected in most cases as well as the long bones; they were short with thickened ends and showed chondrodystrophy. He considered these changes as bringing about a fixation of the thorax at birth, with interference of the process of expansion of the lungs, thus causing death from early asphyxiation. Only the few animals whose ribs were not affected or who incurred only mild deformities lived past this point. Thus, the animals affected seem to have two periods of extreme danger, the first occurring at some unknown point in embryonic development, with resultant death to the majority, and the second at the time of birth. The viability of the heterozygous rabbit seems to be unaffected; growth and development are normal.

Knowledge of the homozygous Pelger state in human beings is limited to a single case report, also from Holland.[70,71] In 1950, these authors saw a two-and-a-half-year-old girl who had had epileptiform attacks since the age of seven months.

Developmental history revealed that she had sat up at the age of eighteen months and walked at two years; and when first seen she spoke only a few words. She was the third child among 6 children; 3 died at an early age — 1 of diphtheria, 1 of diarrhea, and 1 of convulsions. The mother had had 2 abortions. The parents were first cousins. Physical examination of the girl was not remarkable. She had no obvious defects of intelligence, no bony deformities or any other abnormal signs. An electroencephalogram was within normal limits. Blood smears showed 94 per cent of the neutrophils to have a round, eccentric nucleus with a very coarse, fragmented chromatin structure; 6 per cent were indented stab forms. Only 2 neutrophils with segmented nuclei ("spectacle" forms) were found in all the blood and bone-marrow preparations. All eosinophils had round nuclei. Seventy-five per cent of the basophils had round nuclei, and 25 per cent were indented. The nuclei of the monocytes, lymphocytes and plasma cells disclosed a

coarser structure than that usually found. Blood smears showed both parents to have the typical heterozygous Pelger–Huët anomaly. The authors concluded that the striking resemblance between the blood smears of this girl and the homozygous rabbits, in combination with the presence of the heterozygous form in both parents, made it justifiable to assume that the girl represented the homozygous form of the anomaly in man. They similarly concluded that the homozygous form in man is not necessarily lethal, but reminded the reader that the mother had had 2 miscarriages and had also lost 3 children during the first years of life.

Our patient illustrated a typical case of heterozygous Pelger–Huët anomaly. We are able to furnish two additional bits of information on the subject: that the anomaly is not reversible with cortisone, and that no detectable gross or microscopical abnormalities of the human body are related to this anomaly.

One should think of the Pelger–Huët anomaly of the leukocytes in any case in which the total white-cell count is normal and the differential count demonstrates a significant shift to the left with no apparent explanation. The diagnosis depends on recognition of the changes in the granulocytes on the blood smear. As indicated, the heterozygote human being seems to display no specific symptoms of any sort. When there is doubt, the familial occurrence of the anomaly will confirm the diagnosis. However, it should be pointed out that failure to find these changes in other members of the family does not disprove the diagnosis, since the possibility of genetic mutation must be considered.[72] Patau and Nachtsheim[73] have estimated the mutation rate to be about 1:10,000. Undritz's[74,75] concept of partial carriers — in whom some granulocytes show the anomaly whereas others are normal — may be another explanation of such rare exceptions.

Although it is a benign condition, recognition of the anomaly has certain practical significance. Patients may be exposed to the unnecessary expense and inconvenience of numerous diagnostic studies because a marked granulocytic shift to the left is found on a routine blood smear. This situation may also produce iatrogenic disease. One member of the family described above has been under medical care for a "blood condition" for many years. An unrecognized anomaly may also lead to erroneous clinical diagnosis when such a person becomes ill. Therefore, it is important that these persons be informed about the presence and nature of their blood anomaly so that they may furnish this information to their physicians.

Although no conclusive evidence exists regarding impairment of human homozygous patients, the previously quoted rabbit experiments and the single human case report should warn against producing homozygote offspring. Therefore, we think, persons with Pelger–Huët anomaly should not intermarry.

Finally, demonstration of the anomaly may eventually have some medicolegal application for proof of personal identity or in paternity proceedings.[76]

Summary and Conclusions

Pelger–Huët anomaly of the leukocytes consists of arrested segmentation of the granulocytic nuclei at the 2-lobe level. Therefore, one sees an increased number of stab or younger granulocytes, and the rest show 2 segments, with only a rare cell containing a 3-segment nucleus. The total white-cell count remains normal.

The anomaly is inherited as a nonsex-linked single mendelian-dominant characteristic. The heterozygote state is of no pathologic significance. The homozygote state, proved lethal in animals, has been found and reported in only 1 case so far.

A case of heterozygous Pelger–Huët anomaly is reported with negative autopsy findings as related to this anomaly. The problem of the anomaly is reviewed, and the practical importance of its recognition in persons affected is discussed.

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CONSTITUTIONAL HYPERBILIRUBINEMIA*

Its Differential Diagnosis and the Effect of Steroid Therapy

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CONSTITUTIONAL hyperbilirubinemia, or constitutional hepatic dysfunction, is a frequently unrecognized and misdiagnosed form of liver disease, first described in a series of articles by Gilbert and his associates[1-6] in 1907 as "Cholémie simple familiale." Although this disease is often familial, sporadic cases occur and occasionally present an interesting clinical problem in the differential diagnosis of jaundice.

These patients have a mild acholuric jaundice in which hemolytic, hepatic or biliary disease is usually suspected. Most of the cases occur in young adults. The patient may be asymptomatic, but frequently complains of abdominal pain, easy fatigability, anorexia and irritability. The only significant physical findings consist of icterus of the skin and scleras. There is no hepatomegaly or splenomegaly. Laboratory studies are negative except for an elevation of the serum bilirubin, mainly the indirect fraction; there is no bile in the urine. Radiographic study of the gall bladder and liver biopsies are also negative.

Recently, Dubin and Johnson[7] reviewed 4000 liver biopsies from the files of the Armed Forces Institute of Pathology and described 12 cases of chronic idiopathic jaundice, a variety of constitutional hyperbilirubinemia differing from the classic syndrome in that a lipochrome pigment was present in the cells of the hepatic parenchyma; both direct and indirect fractions of serum bilirubin were elevated, and there was associated bile in the urine. The serum of these patients also showed abnormalities in the thymol tur-

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bidity and cephalin flocculation, and the gall bladder was not visualized on cholecystography. Thus, there are laboratory differences in the two varieties, but liver biopsy is diagnostic.

The most important aspect of constitutional hyperbilirubinemia is its consistently excellent prognosis and benign characteristics. It is compatible with a normal, active life. This is true of the classic form of the disease as described by Hult,[8] Comfort,[9-11] Dameshek,[12] Meulengracht[13,14] and others,[15,16] as well as the variety described by Dubin and Johnson.[7]

Unfortunately, too often, in these patients the diagnosis of chronic hepatitis is made, and a superimposed iatrogenic illness or psychoneurosis develops. The case presented below is of this type.

Because of the reported rapid reduction of serum bilirubin in patients with jaundice of various etiologies, and particularly that due to viral hepatitis when treated with steroid substances, it was decided to place this patient on ACTH and later cortisone.[17-20] The effects noted on serum bilirubin will be described later.

Case Report

A 30-year-old government clerk was admitted to this hospital for the 1st time on October 11, 1953, with a chief complaint of anorexia of 3 weeks' duration. He had been intermittently jaundiced for 5 years and had had 3 previous admissions to another Veterans Administration hospital.

He was first noted to be jaundiced by his physician in the course of an examination before operation for a herniated lumbar intervertebral disk in August, 1949. The operation was successful in eradicating the patient's sciatica and pain, but 3 days postoperatively he became quite jaundiced. This jaundice cleared rapidly, and there was no concomitant symptomatology. A complete profile of liver-function studies was not obtained on this admission. The hemogram was normal, and urinalysis was negative. The icteric index was 19.7 units, with a total serum bilirubin of 2.3 mg. per 100 cc. An erythrocyte fragility test gave no evidence of increased fragility.

In spite of occasional mild jaundice he did well and was working on a full-time basis until early in 1951, when he first noticed right-upper-quadrant aching, which was sometimes related to meals, but often was not. This discomfort lasted from a few hours to an entire day and was present for as long as a week, but there never were more than 3 or 4 days without symptoms. The pain did not radiate to the back or shoulder and seemed to be aggravated by heavy meals and fried foods and sometimes by cabbage. He had occasional episodes of chilliness and feverish sensations as often as once a week. In July, 1952, he became more severely jaundiced and noted some darkening of the urine. There was a mild diarrhea, with lighter than normal stools. There was no anorexia or pruritus. He was hospitalized in August, 1952, because of these complaints. At that time he stated that he had never received blood or plasma, nor had he been exposed to jaundiced persons or received any needle punctures. There was no exposure to toxic chemicals.

The past history revealed that he had served with the Army for 2½ years from 1943 to 1945, including service in North Africa and Italy. The only time lost from duty, because of illness, was because of a scalp laceration caused by shrapnel, which had healed without incident. He did not smoke and had never been a heavy drinker. He used no drugs.

The family history revealed that his father had died at 58 of a stroke whereas his mother was alive at 62 years of age and had "gall-bladder trouble." One brother had had viral hepatitis, supposedly acquired in the Pacific. Seven other siblings were living and well. There were no familial diseases. None of the members of his family had had recurrent jaundice.

The patient had had measles, mumps and whooping cough as a child, without complications. Review of the systems revealed that his general health had usually been good before the present illness. For the past 2 months he had noticed occasional temporal headaches associated with reading, and there had been a brief episode of fainting 5 months before this admission.

Physical examination revealed an asthenic, well developed and well nourished man in no distress. He was 162 cm. (5 feet, 10 inches) tall, and weighed 61.2 kg. (135 pounds). The only abnormal physical findings were confined to the skin and the scleras. The abdomen was symmetrical, with a slight icteric tinge to the skin of the anterior abdominal wall. The liver and spleen were not palpable. There was no tenderness, and the peristaltic sounds were normal. There were no spider angiomas and no venous pattern. There was no shifting dullness or fluid wave. There was no ankle edema. In addition to being slightly icteric, the skin showed a mild eczematoid reaction over the dorsum of both hands and in the creases between the thumb and index fingers. The lymph nodes were not remarkable.

The temperature, pulse and blood pressure were normal.

Urinalysis was negative, with a specific gravity of 1.030 and no bile in the urine. Examination of the blood revealed a white-cell count of 7800, with 67 per cent neutrophils, 32 per cent lymphocytes and 1 per cent eosinophils. The blood Kahn test was negative. The hemoglobin was 15.2 gm. per 100 cc., and the hematocrit 46 per cent. The sedimentation rate was 2 mm. per hour. The bleeding time was 1½ minutes, and the coagulation time 4½ minutes; the reticulocyte count was 0.5 per cent, and no spherocytes were seen on peripheral smear. The alkaline phosphatase was 2.25 Bodansky units, and the total cholesterol 231 mg. per 100 cc., with 25 per cent esters.

Stools were negative for blood, ova and parasites.

Liver-function studies showed a total serum bilirubin of 2.65 and 2.7 mg. per 100 cc., a cephalin flocculation of + in 24 and +++ in 48 hours and a prothrombin time of 13 seconds. Additional serum bilirubin determinations on this admission were 2.0, 2.7, 2.4, 2.9 and 3.2 mg. per 100 cc.

The urine was positive for urobilinogen at 1:160 dilution.

X-ray examination of the chest and barium-enema study were negative. An upper gastrointestinal series and an oral cholecystogram were normal.

On this admission a peritoneoscopy with liver biopsy was performed. No abnormalities were seen, and the microscopical sections of the biopsy were reported as normal.

The course was afebrile, and the patient was treated with bed rest and a high-carbohydrate, high-protein, normal fat diet with vitamin supplements. The jaundice cleared, and he was discharged on October 3, 1952.

He was again admitted to the same hospital on March 11, 1953. He stated that after discharge he had felt well and returned to work, followed a diet similar to the one he had received while hospitalized, and had been asymptomatic except for occasional slight right-upper-quadrant pain until 10 days before admission, when he had noticed a decreased appetite and increasing discomfort in the right upper quadrant. The jaundice had again become apparent. There were temporal headaches and some itching of the skin. There were no clay-colored stools, but the urine became darker.

Physical examination was unchanged from the previous admission. Again the skin and scleras had a slightly icteric tinge. The liver was neither palpable nor tender.

Laboratory studies again showed a normal hemogram and negative urinalysis. The blood urea nitrogen was 14.8 mg. and the fasting blood sugar 79 per 100 cc. The total bilirubins were 1.15, 5.8, and 3.4 mg. per 100 cc., and the urine was positive for urobilinogen. The red-cell fragility was normal. A bromsulfalein test showed 2.3 per cent retention of the dye. The total serum cholesterol was 282 mg. per 100 cc., with a cephalin flocculation of + in 48 hours.

A bone-marrow aspiration revealed a normal marrow. The total protein was 7.75 gm. per 100 cc., with 4.6 gm. of albumin and 3.15 gm. of globulin. The thymol turbidity was 1.7 units.

An exploratory laparotomy was performed. The liver was not enlarged. The surface was normal in character. The gall bladder was thin walled and did not contain any calculi. There were no pericholecystic adhesions. The stomach and duodenum were normal to palpation and visualization. The spleen was not enlarged, and both kidneys were normal on palpation. No masses were found within the large bowel. No diaphragmatic hernia was present. The pancreas was soft. The common bile duct was not dilated and on exploration appeared to be patent. The ampulla of Vater felt normal.

A pie-shaped portion of the liver was removed for microscopical study. This section showed the capsule to be slightly edematous. The liver cells contained abundant glycogen. No lesions were seen, and there were numbers of polymorphonuclear leukocytes in the sinusoids. The diagnosis was normal liver.

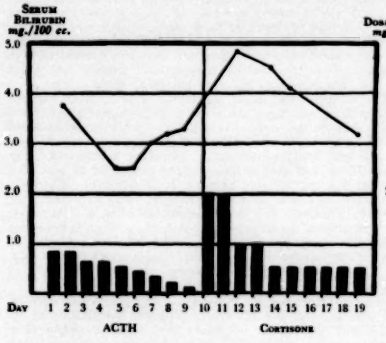

FIGURE 1. *Serum Bilirubin Levels on ACTH and Cortisone.*

The patient was discharged on May 3, only to be readmitted on August 19, 1953, complaining of weakness, abdominal pain and jaundice. Three weeks previously he had noticed a persistent crampy abdominal pain just to the right of the umbilicus. He also complained of insomnia and perirectal pain. The serum bilirubin, which had been determined by a private physician 10 days before admission, was said to have been elevated to 7 mg. per 100 cc.

Physical examination at this time showed the weight to be 124 pounds. There was slight icterus of the skin and scleras and slight tenderness on palpation just to the right of the umbilicus.

Laboratory studies again indicated an elevated serum bilirubin. The basal metabolic rate was −17 per cent on one occasion and +1 per cent on another. The cephalin flocculation was ++.

He was discharged on September 4 on a high-protein, high-calorie diet with multivitamin tablets, and was reassured that his jaundice was probably of no significance. He was advised not to have the serum bilirubin determined more often than every 3 to 6 months. The discharge diagnosis was, as it had been each time previously, chronic hepatitis.

On November 10, 1954, he was admitted to this hospital with the chief complaints of anorexia and right-upper-quadrant pain of 3 weeks' duration. His weight was 57.6 kg. (127 pounds), and the physical findings were unchanged from those previously described. The serum bilirubin was 0.3 mg. per 100 cc. direct and 5.10 mg. total. The cephalin flocculation was +++ in 48 hours, and another determination was negative. The Coombs test was negative. The 48-hour total stool urobilinogen was 375 mg., which is within normal limits.

An oral cholecystogram revealed a normally functioning, well opacified gall bladder. Hemoglobin electrophoresis showed Type A hemoglobin.

Slides of previous liver biopsies were obtained and sent to the Liver Biopsy Registry, Armed Forces Institute of Pathology, for review and were found to be normal by Dr. I. N. Dubin.

The patient was given a regular diet, which was later changed to a high-protein, high-carbohydrate, low-fat diet at his request. A study of the effects of ACTH and cortisone on serum bilirubin levels was performed, with the results shown in Figure 1.

Diagnostic Aspects

This case is typical of the patient with constitutional hyperbilirubinemia. Although we can only speculate regarding the etiology of this condition the repeated hospitalizations, operative procedures and negative liver biopsies represent the concern of the various physicians who attended this jaundiced man and their failure to diagnose his illness, which was most frequently called "chronic hepatitis."

It is also of interest that the patient's jaundice preceded his right-upper-quadrant pain and other gastrointestinal symptoms by at least two years. The most likely explanation for the development of these symptoms is the superimposition of a functional gastrointestinal illness with a strong iatrogenic component. It is our opinion that the patient has an irritable-colon syndrome. Our approach to this problem was an explanation of the syndrome of constitutional hyperbilirubinemia to the patient, with repeated reassurance of its benign nature. At present he is at work on a full-time basis with a minimum of symptoms.

The predominance of the indirect serum bilirubin is characteristic of the classic form of the disease.

The occasional abnormality of the cephalin flocculation probably represents laboratory difficulties inherent in this test rather than hepatocellular disease. The normal cholecystogram proved correct at operation. The normal liver biopsies are also typical findings.

Constitutional hyperbilirubinemia should be suspected in the young adult who is chronically and intermittently jaundiced without significant symptomatology and whose only abnormal physical finding is icterus. The exclusion of obstructive jaundice and hepatocellular disease by the usual studies and of a more subtle hemolytic process by reticulocyte counts and quantitative fecal urobilinogen suggests the diagnosis. A normal liver biopsy gives final histologic confirmation and should leave no doubt in the physician's mind that he is dealing with constitutional hyperbilirubinemia and can give his patient an excellent prognosis.

The variety of this disease as described by Dubin and Johnson[7] should also be kept in mind. Here, there is elevation of the direct as well as the indirect type of serum bilirubin; bile may be found in the urine, and the gall bladder is not visualized on chole-

cystography. Liver biopsy is essential to make this diagnosis and if positive will obviate the necessity for laparotomy.

Steroid Therapy

In view of previous reports of the lowering of serum bilirubin levels in patients with viral hepatitis with the use of adrenocorticotrophic hormone and cortisone,[17-20] a ten-day trial of ACTH was undertaken, with 40 units of an intramuscular preparation twice daily with gradual reduction of dosage to 25 units daily. After this a similar ten-day course of cortisone was given, beginning with 200 mg. daily, with gradual reduction to 50 mg. a day. Daily serum bilirubin determinations were made. There was a transitory fall of serum bilirubin on the fourth day of ACTH to 2.5 mg. per 100 cc. (Fig. 1) from a previously stable level of about 3.2 mg. Cortisone was started immediately after ACTH was discontinued. The patient was unchanged clinically on ACTH or cortisone except for a marked improvement in the dermatitis of the hand. It appears that steroid therapy had little, if any, effect on the jaundice of constitutional hyperbilirubinemia in this case. Chalmers and his associates[21] found slight drops in the serum bilirubin in patients with this condition treated with ACTH. In their cases there was no increase in measurable urobilinogen excretion, indicating the possibility that the effect of ACTH on bilirubin metabolism is occasionally a choleretic one. This group also treated patients with proved extrahepatic obstruction, and in 4 of 9 cases the serum bilirubin dropped after ACTH was given.

Summary

A case of intermittent jaundice of five years' duration and the criteria for diagnosis of constitutional hyperbilirubinemia are reported.

The importance of diagnosis of this disease to prevent unnecessary hospitalizations, operations and iatrogenic illness is stressed.

The effect of steroid substances on the jaundice in this case is discussed. Unlike some cases of jaundice due to hepatic or obstructive disease, in which steroid substances tend to lower the level of serum bilirubin, no significant effect was noted in the case reported.

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EPIPHYSEAL INJURY FOLLOWING FROSTBITE

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BOSTON

BONE changes in frostbitten extremities have been described only rarely in the medical literature, and before World War II, most cases documented by radiographic studies were from Europe. In a recent article Vinson and Schatzki[1] carefully reviewed the x-ray findings in 100 soldiers who received frostbite injuries during the Korean conflict. Sixty-four of the patients, all young men whose epiphyses were already fused, showed some abnormality of bone during the period of x-ray observation. The case presented below, that of a child of seven, seems worth recording because of the striking roentgenographic changes demonstrated in a hand that had been frostbitten five years before.

Severe cold injury to the hands or feet is not common; it was formerly considered a disease of fishermen, hunters and vagrants. However, during the early months of World War II numerous cases were reported by the British among the survivors of marine

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disasters. Later, the American literature described cold casualties in both ground and air-force personnel. Although the clinical findings and treatment of such injuries are similar, it is common practice to classify them according to the conditions under which they were received. Trenchfoot[2] is sustained by soldiers who are immobilized in moist cold, at temperatures above freezing. Immersion foot, or hand,[3] results from a prolonged exposure to cold water, whereas frostbite[4] describes the injury received by tissue when it is actually frozen in an environment of dry cold.

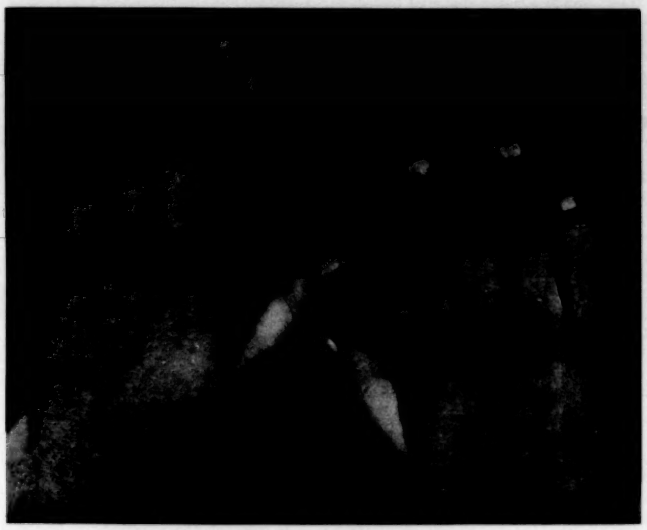

FIGURE 1. *Hands of a Seven-Year-Old Girl, Five Years after Frostbite (Note the Short, Broad Distal and Middle Phalanges on the Right).*

The major interest in frostbite has been in defining proper therapy for the soft-tissue damage. The apparent paucity of significant bone changes in the cases reported in the American literature is probably explained by the failure to obtain long-term radiographic follow-up study. During the early stages of healing a transient osteoporosis of the involved digits has been noted occasionally, as well as necrosis of bone beneath the injured soft tissues. Once the soft tissues have healed, the underlying bone, when not initially destroyed, has often been overlooked as a site for still further abnormal change.

Vinson and Schatzki[1] have shown that the late bone lesions, which are detected at the articular surfaces of the phalanges, do not become apparent until three to eight months after injury. Seven of their cases showed abnormalities in 25 joints. These changes were characterized by small, rounded, punched-out areas of demineralization at the phalangeal joint surfaces, frequently communicating with the joint space. The severity of these arthritic lesions could not be correlated with the initial degree of frostbite.

From Germany, in 1930, Löhr[5] reported the case of a sixteen-year-old boy whose hands were severely frostbitten while gripping the handlebars of his bicycle in sub-zero weather. The typical soft-tissue changes of edema, vesiculation and loss of fingernails were present. Nine months later he again sought medical attention because of pain, swelling and limitation of motion in the involved distal joints. X-ray examination disclosed articular changes similar to those recently described by Vinson and Schatzki.[1] In addition, the distal phalangeal epiphyses of the third, fourth and fifth fingers and the middle phalangeal epiphyses of the fourth and fifth fingers of both hands were partially or completely destroyed.

Bennett and Blount[6] reported a similar case in 1935, as did Thelander[7] in 1950.

The following case demonstrates the late changes that may be detected roentgenographically in both the articular areas of bone and the epiphyses.

CASE REPORT

E.N. (M.G.H. 877245), a 7-year-old girl, was first seen in the Orthopedic Outpatient Department in January, 1955,

because of finger deformities. In March, 1950, at the age of 2½ years, she wandered out of the house with her dog and onto a snow-covered road in Saskatchewan at 5 p.m., when the temperature was below 0. When found, about 2 hours later, she was wearing woolen leggings and a sweater but was without hat or gloves; her left hand was in a pocket. Her father immediately noticed that the fingers of both hands, particularly the right, were white and the tissues stony hard. Ice could be scraped from the skin surface. There was no apparent pain. The hands were thawed in cold water for 60 to 90 minutes, after which there was considerable pain, worse in the right hand than the left, and the tissues gradually became swollen and developed a mottled pink to blue discoloration. The attending physician applied a bland salve and wrapped each finger and hand separately.

On the following day, vesiculation extending from their tips to the proximal interphalangeal joints appeared in the skin of the 2d, 3d, 4th and 5th fingers of the right hand. During the next several weeks, the swelling, blistering and pain subsided, but the skin over these fingers became dry and hard and turned a dark brownish black. The only treatment was a daily application of ointment and change of dressing.

At about the 3d week, the fingernails of the involved 4 fingers became detached, and the skin down to the proximal interphalangeal joints "peeled off, like a glove," revealing a delicate covering of pink skin. At no time was there any evidence of infection. The left hand showed none of these changes.

Five or 6 months after the frostbite, the mother noticed flexion deformities of the distal interphalangeal joints of the 2d through 5th fingers of the right hand; these have progressed very gradually. About a year later, it was first noted that the fingers of the right hand, especially the distal phalanges, were shorter than those of the left. No difference in function between the 2 hands and no change in color after exposure to cold had been observed. The patient had never complained of cold sensitivity of the fingers, and, in fact, the mother believed that the right hand usually felt warmer than the left.

Physical examination showed a co-operative, healthy-appearing girl. The color, temperature and pulses of both hands were equal and normal, and there was no evidence of increased or decreased sweating of either hand. The left hand appeared normal. With the right hand at rest, there was slight flexion of the distal interphalangeal joints of the 2d through 5th fingers, most marked in the 3d and 5th fingers (Fig. 1). There was also some radial deviation of the distal phalanges of the 4th and 5th fingers. The distal phalanges of the 3d, 4th and 5th fingers appeared clinically shorter and broader than those on the left, as did the middle phalanges of the 4th and 5th fingers. The distal interphalangeal joints of these fingers were thickened, and there was dorsal prominence of the 3d distal phalanx at the proximal end.

FIGURE 2. *X-Ray Film of the Same Patient (Note the Partial or Complete Absence of 6 Phalangeal Epiphyses on the Right — 2d-5th Distal, and the 4th and 5th Middle).*

Actively, the distal interphalangeal joints of the 2d through 5th fingers on the right lacked 5, 30, 20 and 60° of full extension respectively. All these joints, however, could be passively extended to neutral, and the radial deviations could be passively corrected. There was full flexion of all the joints, and function was excellent, with smooth motion and no grating or crepitus. Although the patient could distinguish sharp from dull pain, there was moderate hypesthesia over the volar aspect and minimal hypesthesia over the dorsal surface of the distal phalanges of the 2d through 5th fingers, more marked in the 4th and 5th fingers.

X-ray examination (Fig. 2) was reported as follows:

The bone age is approximately 6 years and 10 months, according to Todd's standards, which corresponds to the stated chronologic age of 7 years. Bone density and architecture of the left hand appear to be entirely normal. There are, however, striking, abnormal changes in the right hand. The distal phalanges of the 3d, 4th and 5th

fingers are shorter than those of the left hand; the middle phalanges of the 4th and 5th fingers are also shorter and broader than their opposite members. The trabecular pattern is accentuated. The most significant change is the complete absence of the epiphyses normally accompanying the distal phalanges of the 3d, 4th and 5th fingers, as well as that of the middle phalanx of the 5th finger. A tiny fragment of the secondary ossification center of the epiphysis of the distal phalanx of the 2d finger is present and also a portion of secondary ossification center of the epiphysis of the middle phalanx of the 4th finger, which is partially fused with the shaft. In addition, at the articular surfaces there are numerous small, rounded areas of demineralization of a "punched-out" nature. There is flexion deformity of the distal interphalangeal joints of the 2d through 5th fingers on the right, more marked in the 3d and 5th fingers. The remaining bones of the right hand are normal.

X-ray measurements of phalangeal length were made by means of posteroanterior and lateral films, the latter to obviate the error due to flexion contractures of the distal phalanges. These measurements showed that the distal phalanges of the index fingers were of equal length, the distal phalanges of the right 3d and 4th fingers and the middle phalanx of the right 4th finger were 0.3 cm. shorter than the left, the distal phalanx of the right 5th finger was 0.25 cm. shorter than the left, and the middle phalanx of the right 5th finger was 0.4 cm. shorter than the left. Measurements were made to include the entire ossified portion of the phalanx, which included secondary ossification centers where present.

The report from the Vascular Laboratory was as follows*:

> In a constant-temperature room at 77°F. both hands were placed in an insulated box maintained at 46°F. for 30 minutes. No significant difference in the digital skin temperature or digital plethysomographic pulsations of the 2 hands was noted during this period. A normal amount of gradual cooling and vasoconstriction occurred. Before the hands were exposed to cold, however, in a room at 77°F., it was found that the digital skin temperature of the involved hand remained 3° to 4° higher than that of the normal one. The difference was established on 2 separate occasions. This limited study suggests that no sensitivity to cold exists in the involved hand under these conditions.

Summary and Conclusions

A case in which classic frostbite in a two-and-a-half-year-old girl had been accompanied by injury to 6 of the 14 phalangeal epiphyses of the right hand is presented.

The x-ray appearance, as well as the phalangeal measurements, indicates that the injury to the distal phalanx of the right index finger was not severe enough to affect the growth potential of the epiphyseal cartilage during the five years since frostbite. However, the distal phalanges of the right third, fourth and fifth fingers, and the middle phalanx of the fifth finger, in which there is complete absence of the epiphyses, show no growth in five years when compared with the left hand and with serial films of normal children in the same age group. The middle phalanx of the right fourth finger shows a discrepancy in length that is somewhat less than would be expected if there had been complete destruction of the epiphysis and no growth. This is in keeping with the x-ray finding of a partially fused fragment of the secondary ossification center of this phalanx.

The range of epiphyseal injury, and subsequent growth retardation, is probably related to the degree of vascular damage secondary to frostbite. Whether the hypothermic injury not only compromised the circulation but also caused death of the cartilage cells of the epiphyses by the direct effect of freezing is unknown. The patient has not given clinical or laboratory evidence of cold sensitivity in the hand, which has been reported after frostbite.

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*Examination by Dr. C. V. Menendez.

MEDICAL PROGRESS

ABDOMINAL SURGERY

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THE last report on this subject in the *Journal* appeared two years ago. For this review papers have been studied that either are outstanding or are indicative of particular trends in abdominal surgery. It should be realized that only very brief abstracts can be presented and that this survey is merely a guide to many contributions that should be studied in their original form.

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Stomach

Cancer

Total gastrectomy as a routine operation for cancer has continued to lose popularity. In a survey of opinions of many leading American surgeons on the subject of superradical cancer surgery, Fisher[1] reported that not one favored total gastrectomy as a routine.

Disappointment has also attended the even more

extensive operations. McNeer and Pack[2] have found that their "extended radical gastrectomy" now carries an operative mortality of 26.3 per cent. This operation includes resection of the distal half of the pancreas and spleen together with the stomach. Anastomotic leaks accounted for nearly half the deaths. This operation has been abandoned by them in favor of more conventional procedures when the cancer is in the distal portion of the stomach, though it is still used for cancer of the fundus.

One type of carcinoma for which total gastrectomy is particularly indicated is that associated with pernicious anemia, according to evidence presented by Schell, Dockerty and Comfort.[3] Ninety-four cases were observed in the Mayo Clinic. These carcinomas differ from the usual gastric cancers in that they tend to be polypoid and located in the fundus or cardia, are multicentric in origin and of lower average grade or a mixture of grades, and cause symptoms very late.

MacDonald and Kotin[4] have emphasized some well known facts about gastric cancer by the use of more impressive nomenclature. "Biologic pre-determinism" (that is, the characteristics of the tumor itself) rather than the type or time of surgical treatment is of overwhelming importance in determination of the end results in gastric carcinoma. The authors believe that less than 20 per cent of all gastric cancer is surgically curable, and that the only genuine "early" treatment is gastric resection for gastric ulcer that actually is carcinoma.

Replacement procedures are being used more frequently throughout the country. There is, at present, no evidence that they improve postoperative nutrition, and certainly they contribute to an increased mortality. Since adequate controls are impossible in man, Kelly and Wangensteen[5] carried out studies on dogs. The dog tolerates total gastrectomy less well than man, since severe nutritional disturbances and anemia generally occur and terminate in death. However, the length of survival was found to be distinctly longer when gastroduodenostomy was used after total gastrectomy rather than gastrojejunostomy. Substitute reservoirs with a large capacity made from the jejunum were of no apparent benefit to the animals in terms of reduction of weight loss or survival.

Other Tumors

Next to cancer, malignant lymphoma is the most common type of gastric tumor. Allen and his associates[6] found 79 cases of lymphoma apparently primary in the gastrointestinal tract in a forty-year period at the Massachusetts General Hospital. In the stomach they comprised 2 per cent of the tumors, with a five-year survival after surgery of 58 per cent. In the small bowel, 40 per cent of the tumors were lymphoma, with a survival rate of 33 per cent. The corresponding values for the colon are 0.5 per cent and 0 per cent. Although the value of postoperative x-ray therapy is not clear, five-year survivals have been noted when the resected specimen has shown involvement of lymph nodes or resection margins, and x-ray therapy has been used.

Leiomyosarcoma of the stomach is an uncommon but also an important tumor. Though only 135 cases have been reported in the literature, Giberson, Dockerty and Gray[7] have studied 40 more from the Mayo Clinic. They reported a five-year survival of 53.8 per cent. The classic symptoms were those of abdominal distress, gastrointestinal hemorrhage and the presence of an abdominal mass.

Gastric Ulcer

A large number of follow-up studies of treated gastric ulcer now are available; of these a very careful study by Gott, Shapiro and Kelty[8] should be cited. Their incidence of cancer in apparently benign ulcer was estimated at 9 per cent. Of the benign ulcers, 55 per cent healed in four, and 88 per cent in six weeks; the older patients showed slower healing and more frequent recurrence.

Massive Hemorrhage

Although many papers have appeared on the problems of massive hemorrhage from the upper gastrointestinal tract, one of the most interesting facets has been that of the treatment of the patient with such hemorrhage who is operated on and in whom no definite lesion is encountered. Gray, Shands and Thuringer[9] found 48 such patients in the Mayo Clinic. Twenty-eight of them had surgical exploration only, and 63 per cent of this group had recurrent hemorrhage within five years. Twenty patients had partial gastrectomy, and only 11.7 per cent had recurrent hemorrhage. In 8 of these 20, a definite lesion was found, but in the remainder there were only varying amounts of chronic gastritis. The authors' recommendation for partial gastrectomy in these patients with massive bleeding from an indeterminate source is, in the opinion of most surgeons who have been faced with this problem, a wise one.

The early use of diagnostic technics in patients with massive hemorrhage has long been advocated by Tanner in England. In this country they have been less popular. An indication of their value has been furnished by Palmer and Scott,[10] who carried out a vigorous diagnostic approach in 163 patients. This involved esophagoscopy in 105, gastroscopy in 136 and fluoroscopy in 159. The bleeding lesion was identified in 83 per cent of the patients. No dangers were encountered from this method of diagnosis. Twenty-nine of these patients then had emergency surgical therapy.

Duodenum

Ulcer — Acute Perforations

Cooley et al.[11] studied a series of 199 patients.

The operative mortality for 112 cases treated by primary subtotal gastrectomy was 4.5 per cent, and that for 70 treated by simple closure was 8.6 per cent. Primary gastric resection is now advocated for all patients with perforations of gastric ulcer, and in those with duodenal ulcer who have other complications or a long history of ulcer disease.

Definitive Therapy for Ulcer Disease

The main trends in definitive surgery for the treatment of ulcer indicate decreasing popularity of vagotomy and gastroenterostomy, and an increased use of vagotomy with some type of gastric resection. Meanwhile, the various operative sequelae of partial gastrectomy have been subjected to more searching investigation.

The decline of the popularity of vagotomy alone, or in conjunction with gastroenterostomy, has stemmed from several long-term studies, such as that by Brooks and Moore[12] and by Hoerr.[13]

Brooks and Moore, in a study of 132 patients with a follow-up period of six to ten years, found return of parasympathetic activity in many patients in whom previous studies had indicated a complete vagotomy. Recurrent ulcer may occur while physiologic effects of vagotomy persist. Present-day laboratory tests have no consistent correlation with clinical results in the evaluation of surgery for duodenal ulcer. On the other hand, vagotomy gave good clinical results when performed for postresection anastomotic ulcer.

Hoerr[13] followed 145 patients who had been treated by vagotomy and posterior gastroenterostomy for duodenal ulcer. The failure rate showed a steady rise throughout all years studied, with only 8 failures noted after a year, but 21 at the fifth year. Consequently, he has given up the operation except when resection has apparently seemed too hazardous. The recurrence rate seemed to be just as high in patients in whom the most careful technic had been used.

It is only fair to state that many surgeons still cling to their belief in the efficacy of vagotomy and posterior gastroenterostomy despite such evidence as that presented above, as indicated by the discussion of Hoerr's article.

More late follow-up studies of patients who have had partial gastrectomy for ulcer have appeared. One of the most important of these was by Harvey, St. John and Volk.[14] Three hundred and ninety-four patients were followed for more than five years after operation. It is noted that a patient who had had a continuously satisfactory result for five years rarely manifested symptoms thereafter. In those followed for this time, 83 per cent of resections for duodenal ulcer and 71 per cent of those for gastric ulcer were always satisfactory. In this group surgical complications and recurrent ulcer furnished the most important causes for unsatisfactory results, recurrent ulcers having been noted after 4.5 per cent of all resections for duodenal ulcers. Comparison with a more recent group of patients who had had resections shows that surgical complications have become much less frequent, but the dumping syndrome is much more prominent. The authors believe that the more radical resections that are now being used have not reduced the percentage of recurrence but have increased the number of patients with late digestive symptoms.

Another late survey of 749 patients three to twelve years after a Billroth II gastrectomy was made by Troell.[15] The over-all results were as follows: mortality from operation, 3 per cent; late deaths from other causes, 2 per cent; untraced patients, 4 per cent; recurrent ulcer, 1 per cent; severe postprandial symptoms, 3 per cent; and improvement, 87 per cent.

The Billroth I operation has found a strong advocate in Harkins. He and his collaborators[16] have carried out 291 such anastomoses. A measured 73 per cent of the stomach was removed in 73 per cent of the patients. Early results showed an operative mortality of 2.6 per cent when the operation was done for benign disease. The morbidity rate was 30 per cent. Early follow-up results indicated that 92 per cent had a satisfactory result.

Postgastrectomy Symptoms

Out of many papers published on postgastrectomy symptoms, one of the most practical and valuable contributions has been made by Hayes.[17] He found that after a gastrectomy the inhibiting effect of a high-fat diet on gastric evacuation is lost. Therefore, a diet that is high in fat, high in protein content and low in carbohydrate is fed to patients with postgastrectomy symptoms. These proportions in caloric value are, respectively, 5, 1.5 and 1. Hospital care is necessary for proper administration of the diet. He studied 7 cases who had lost an average of 25 per cent of their preoperative weight after gastric resection. All but 1 patient, who is still under observation, were returned to their preoperative weights, and meanwhile postgastrectomy symptoms were controlled completely.

The late sequelae of gastrectomy include an increased expectation of pulmonary tuberculosis. This has been noted by Warthin[18] and Allison,[19] who observed that the average interval between operation and active tuberculosis was four years.

Anastomotic Ulcer

The postoperative anastomotic ulcer can be practically eliminated if bilateral vagotomy is added to the standard 75 per cent gastrectomy, but it is done at the price of an increased occurrence of postgastrectomy symptoms and a more difficult convalescence. For example, Palumbo, Mazur and Doyle[20] found a rate of 1.3 per cent of stomal ulcers after standard resections; when vagotomy was added there

was persistent achlorhydria and no recurrent ulcer.

The treatment for anastomotic ulcer when it occurs after gastroenterostomy is generally conceded to be gastric resection. When the ulcer occurs after an adequate resection, vagotomy has carried a lower mortality than reresection, and therefore has usually been preferred. Wells[21] collected 120 cases of anastomotic ulcer from the London hospitals, though only 39 satisfied his rigid criteria. Vagotomy performed for anastomotic ulcer occurring after partial gastrectomy gave good results in only 2 out of 3 cases, but still was the preferable operation from the point of view of mortality.

Marshall and Markee[22] studied 172 surgically proved stomal ulcers: 77 per cent of them followed gastroenterostomy. When the ulcer occurred after adequate gastrectomy, a trial of medical therapy was given. After reoperation the ulcer recurred in about 6 per cent of patients. Total gastrectomy was required for control in 2.

From the Mayo Clinic Walters, Chance and Berkson[23] reported a study of 301 gastrojejunal ulcers. When the ulcer occurred after gastroenterostomy, gastric resection gave excellent results in 86.5 per cent of the patients. When the ulcer occurred after gastric resection, vagotomy combined with gastric resection gave excellent results in all the 9 patients followed.

Diverticulitis

Though the diagnosis of duodenal diverticula had been made 525 times in thirteen years at the Mayo Clinic, only 20 patients had an operation for them, according to Waugh and Johnston.[24] There were 2 deaths. The authors believe that diverticular hemorrhage is extremely rare, that radiology does not aid greatly in determining which diverticula cause symptoms, and that less than half the few patients who have a radical operation can be said to have had an excellent result.

Intestine

Jejunal Replacement

Within the past few years segments of jejunum have been transplanted into so many spots that the casual reader may wonder if nature had not erred in not putting them there originally. Most of the enthusiasm stemmed from Henley's[25] report. He found an extraordinary relief of postgastrectomy dumping symptoms, including a weight gain in 97 per cent of 110 patients, by the interposition of a jejunal loop between the gastric remnant and the duodenum. Consequently, many other surgeons have used this method, and often their response has been far less than enthusiastic.

For example, Brooke[26] has reported recurrent ulcers in a third of the transplanted jejunal loops. Tanner[27] believes the good results are due to gastroduodenal continuity, rather than to the jejunal loop. Everson et al.[28] reached the same conclusion by experiments on dogs, which, they found, tolerated a Billroth I anastomosis much better than a Billroth II; the insertion of the jejunal loop did not improve nutritional status any further. This suggested that the jejunal tube acted merely as a conduit.

The use of a transposed jejunal segment to connect esophagus and stomach has been employed by Merendino and Dillard[29] after resection of the lower esophagus for reflux esophagitis, cardiospasm and esophageal varices. Experimental data have indicated that such a segment has greater resistance to acid-pepsin digestion than either esophagus, stomach or duodenum.

A Roux-Y loop of jejunum has been used widely by Allison and DaSilva[30] to sidetrack the stomach since mediastinal esophagogastric anastomoses have been so unsatisfactory in the treatment of hiatus hernia and reflux peptic esophagitis that they have been abandoned. Twenty-eight such anastomoses were reported for benign lesions, chiefly stenosis from esophageal peptic ulcer. Twenty-seven patients survived; 19 of them feel well and eat normal, but slightly smaller, meals. The others have pain after meals, the dumping syndrome or anemia.

Regional Enteritis

An interesting observation has been made by Davis, Dockerty and Mayo,[31] who have found that patients with regional enteritis have roughly three times as many cells in the myenteric plexus as normal persons. This increase is not confined to grossly involved portions of the bowel, but is found in apparently normal bowel as well. The number of such cells increases in proportion to the length of time the patients have had their disease. It may be noted here that a similar increase in such cells in the myenteric plexus of the colon has been found in ulcerative colitis by Storsteen, Kernohan and Bargen.[32] Absence of these cells in isolated segments of the colon leads to typical Hirschsprung's disease. Swenson and Fisher[33] have found in 2 out of 150 such patients that the entire colon lacked such cells, and in these cases the whole colon must be resected with the formation of an ileoproctostomy. Congenital megaduodenum has also been associated with absence of ganglion cells in that section of the intestine (Barnett and Wall[34]).

Van Patter and his associates[35] have reviewed 600 cases of regional ileitis treated at the Mayo Clinic; 402 patients had definitive surgical procedures. The disease was known to be arrested for at least two years in half the followed patients. Their procedure of choice is primary resection of the lesion followed by end-to-end anastomosis. Exclusion procedures often are not followed by good results.

Function of Ileum and Jejunum

The comparative importance of the proximal and distal small intestine for nutrition was evaluated in dogs by Kremen, Linner and Nelson.[36] Sacrifice of the distal 50 per cent of the intestine produced profound interference with fat absorption, particularly when the ileocecal valve was removed. With removal of a comparable length of the upper small bowel the animal's weight was maintained, and no great interference with fat absorption was observed.

Intestinal Obstruction

An extensive and authoritative discussion of the entire subject is given in a new edition of Wangensteen's monograph.[37] The trends that are of interest include the development of technics whereby operation is carried out with less delay. These usually involve some form of operative decompression of the intestine. For this purpose several new instruments have been devised, such as those of Cantor[38] and Barnes.[39]

In infants and children resection of obstructing lesions and primary end-to-end anastomoses are gradually replacing exteriorization procedures. Swenson[40] reported on 32 infants treated in this fashion, with only 3 deaths. Technical details include anastomosis made with a single layer of silk mattress sutures, aseptic aspiration of the distended proximal intestine, and saline distention of the collapsed distal loop to facilitate anastomosis. A similar operation is used by Gerrish,[41] who adds a catheter enterostomy just proximal to the anastomosis, and by Benson.[42]

The Noble plication procedure has attracted a great deal of attention recently. Although most reports are favorable, it must be noted that these series of patients have no comparable set of controls. Smith[43] has used it on 39 patients, with 1 postoperative death. Fifteen had a total plication, and 2 of them required reoperation for subsequent obstruction. Thirteen patients had a partial plication, and 3 had recurrence of obstruction. Seabrook and Wilson[44] had 5 failures in 57 cases, and in 3 of the failures of these patients a revision or extension of the plication produced a good result.

The methods of treatment of intestinal obstruction in the University of Minnesota Hospital have been summarized by Smith, Perry and Yonehiro.[45] In 1252 cases the mortality was 12.5 per cent and that attributable to the obstruction was 7.5 per cent. They advocate a twelve-hour trial of suction for nonstrangulated small-bowel obstruction with continuation only if improvement is secured; treatment of obstructed lesions of the ascending colon by aseptic decompression of distended small bowel followed by resection and primary anastomosis; immediate resection and anastomosis for other obstruction of the colon in the young, and transverse colostomy followed by later resection for other obstructions in the older, and immediate operation for all strangulating obstructions.

Dennis[46] has summarized current procedures in the management of obstruction of the small intestine. Every attempt is made to operate on these patients within four hours of entry to the hospital.

An undercurrent of dissatisfaction with intestinal decompression by the long intestinal tubes is apparent, particularly because of the delay that often follows their use. A critique of decompression is given by Paine,[47] who prefers to use a weighted Levin tube.

Intestinal Obstruction and Peritonitis

An extremely lethal type of intestinal obstruction is that associated with peritonitis. For these patients Welch[48] advocates a radical operative approach designed primarily to restore intestinal function. This method has been described and used in 15 patients, with 13 survivals.

Appendix

Acute appendicitis in the presence of pneumoperitoneum has been observed in 31 cases by Raiford and Thompson.[49] In these patients rebound tenderness, rigidity and muscle guarding were conspicuously absent. Tenderness to direct pressure was the most constant physical sign.

Colon, Rectum and Anus

Acute Obstruction

In addition to the more or less routine disagreement between the advocates of cecostomy and transverse colostomy, an additional method of therapy for acute large-bowel obstruction is now being used in several areas. This involves immediate resection and anastomosis without preliminary operative decompression. The arguments in its favor are well presented by Gregg,[50] who resected 16 perforating or obstructed lesions, with no deaths.

Comment on this method is also provided by Smith et al.,[51] who discuss 208 patients with obstruction from cancer of the colon. There were 30 deaths, which were due chiefly to the delayed treatment of cecal cancer and to primary resection of the descending colon in the presence of severe distention. Primary resection was carried out in 67 per cent of the lesions of the descending and 96 per cent of those of the ascending colon.

It is clear that if primary resection is to be employed for acute colonic obstruction, the surgeon must be extremely cautious, or he may convert an operation that is simple and safe in two stages to one that is entirely unsatisfactory or fatal because of technical considerations.

Cancer

Two very important contributions on the mechanism of postoperative recurrence of cancer of the

colon have been made by Cole and by Turnbull. McGrew, Laws and Cole[52] have proved that local implantation of cancer within suture lines is due to mechanical manipulation of the bowel at the time of surgery, whereby viable tumor cells are massaged freely into the lumen of the colon. Ligature applied about the colon above and below the tumor before mobilization will prevent this dissemination beyond the ligatures; without the ligatures positive cells were found within the lumen of the bowel as far as 35 cm. from the tumor.

Mechanical dissemination through the blood stream by such manipulation was investigated by Fisher and Turnbull.[53] They recovered tumor cells from the blood of the major mesenteric venous channel in 8 of 25 specimens of colorectal cancer by a perfusion technic. Hence, venous ligation preliminary to tumor mobilization is logical.

The discussion of the value of aortic ligation of the inferior mesenteric artery continues. McElwain, Bacon and Trimpi[54] describe 150 patients with cancer of the colon, rectum or anus who had this procedure. The specimens for accurate lymph-node section were cleared in 90. In at least 8 of these cases a ligature of the inferior mesenteric artery below the left colic branch would have failed to remove positive nodes. Follow-up results are not available to know how many of these 8 patients have been cured.

Rossi[55] also studied lymph-node spread in a similar group of patients. Eight per cent of the resected specimens showed involved nodes within 1 cm. of the origin of the inferior mesenteric artery; 14 per cent were within 2 cm., and 22 per cent within 3 cm. In his hands, the additional procedure of ligation of the artery at its source has not led to any deaths.

The frequency of venous spread of cancer determined on microscopic examination of resected specimens has been accepted as about 20 per cent. However, Barringer and his associates[56] found a rate of 38 per cent by preliminary injection of a radiopaque substance into the venous bed of the tumor to direct the selection of tissue blocks.

Most collected data on survival of patients with cancer have been from large hospitals. Now an extensive community survey involving the whole state of Connecticut, where cancer is a reportable disease, has been made by Ottenheimer and Oughterson[57]; 7699 cases of cancer of the colon and rectum, the most common malignant tumor, were reported from 1935 to 1949. They observed that patients now are not admitted with earlier stages of the disease than they were ten years ago, but that progress has resulted from the fact that more surgeons do more radical operations. Of these patients who had limited surgery for cure (mostly local excision of malignant polyps) 60 per cent failed to survive for five years, indicating that a more radical operation is indicated for these small lesions. The estimated five-year survival free of disease for all patients is now 19.4 per cent, whereas for those who had survived radical resection for cure it is 44.6 per cent.

Grinnell[58] has analyzed 49 cases of squamous-cell cancer of the anus seen in the Presbyterian Hospital, New York City. The absolute five-year survival was 36.8 per cent. Since 1943 the use of radiation except in palliative therapy has been abandoned. Abdominoperineal resection is best; local excision is not recommended even for very small tumors. Metastatic lymph nodes along the superior hemorrhoidal vessels were found in 28 per cent of resected specimens; metastases to inguinal lymph nodes were infrequent and occurred only late in the course of the disease.

Ulcerative Colitis

The combined operation of ileostomy and total colectomy, performed in one stage, is winning wide acceptance. An illustration of the effectiveness of this therapy is demonstrated by Ripstein[59] in his discussion of perforation of the colon from this disease. In 5 cases of this most severe complication treated by ileostomy and local drainage there were 3 deaths. Of 11 patients treated by primary resection of the colon, none died. He notes that a distended loop of colon demonstrated by x-ray study in the absence of small-bowel distention is a reliable sign of impending perforation.

A typical example of this newer attitude is given by Scarborough.[60] In the past two years, out of 20 patients treated, 19 had a complete coloproctectomy and simultaneous ileostomy, and only 1 had a two-stage procedure. There were no operative deaths.

The mechanism of ileostomy dysfunction has been studied by Turnbull and Crile.[61] They have eliminated this complication by turning down a rim of projecting mucosa on the ileostomy with suture to the skin. In 21 patients treated in this way only trivial complications were encountered, and no postoperative dilatations or tube insertions were required.

The life of the ileostomy patients has been made much easier by the formation of groups of patients who have had this operation. They discuss and disseminate information. Their work has been invaluable to patients and doctors alike. The activities of the Boston group have been described by Lenneberg.[62]

The late follow-up results of patients treated for ulcerative colitis in the Massachusetts General Hospital are summarized by Wheelock and Warren.[63] Three hundred and forty-three patients were followed for ten years, or until death. Forty-eight per cent eventually required operation. The first postoperative year is by far the most difficult. For example, of 26 admissions for postoperative small-bowel obstruction, all but 1 occurred within a year of operation. Cancer of the colon developed in 31 patients, with only 2 five-year survivals; of the patients who had survived for ten years after onset of the disease and had not had their colons removed, the rate was 18.1 per cent.

Injuries

Injuries of the colon and rectum were treated regularly during World War II by exteriorization procedures. Evidence is accumulating that this practice is not necessary in civilian life, where time lag is shorter and there is no problem of early evacuation. Tucker and Fey[64] reported 42 cases of penetrating wounds of colon and rectum treated in the Shreveport Charity Hospital, with a mortality of 14.3 per cent. Seventeen cases had primary closure with no mortality; this group comprised, in the main, patients with wounds treated within six hours of injury and not over 5 cm. in diameter.

The same opinion is voiced by Woodhall and Ochsner[65] and by Christensen, Ignatius and Mathewson.[66] The latter group report 23 cases of penetrating injury of the large bowel seen on the Stanford Surgical Service in twelve years. Eight were treated by suture alone and healed uneventfully; the authors believe that 7 others could have been treated in that way.

(To be concluded)

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MEDICAL INTELLIGENCE

ADVANTAGES OF PYRIDOSTIGMINE BROMIDE (MESTINON) AND EDROPHONIUM CHLORIDE (TENSILON) IN THE TREATMENT OF TRANSITORY MYASTHENIA GRAVIS IN THE NEONATAL PERIOD*

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THIS paper emphasizes the value of recognizing the symptoms of myasthenia gravis, so that appropriate treatment may be given to save the lives of these newborn infants whose mothers have myasthenia gravis. The occurrence of transitory myasthenia gravis in a considerable number of the offspring of women with myasthenia gravis has been described by several authors.[1,2] In a review of this disease Kibrick[3] adds 6 cases to those previously reported.

Treatment of such infants by neostigmine (Prostigmin) has been reported as being generally satisfactory, but has not been ideal as evidenced by the fact that some of the babies thus treated have died. The undesirable side effects of this drug have been serious enough to stimulate the search for other drugs to replace neostigmine. Improvement in the therapy of myasthenia gravis in adult patients by the use of pyridostigmine bromide was reported by Osserman and his co-workers.[4] The same group demonstrated the method of determining the optimal dose of pyridostigmine or of neostigmine by administration of test doses of a short-acting cholinergic drug called edrophonium chloride.[5]

The case reported below demonstrates the advantages that were achieved by the use of pyridostigmine bromide† and edrophonium chloride‡ in a newborn infant with severe myasthenia gravis — in this case the substitution of pyridostigmine for neostigmine was probably life saving. This is the first published report of the use of these drugs in the treatment of a newborn infant with transitory myasthenia gravis.

CASE REPORT

D.B., weighing 2.8 kg. (6 pounds, 5 ounces), was born at term on December 8, 1954. The mother, a 24-year-old primipara, had had myasthenia gravis since she was 16 years of age. She took 6 to 12 tablets (15 mg. per tablet) of neostigmine daily, usually averaging 8 tablets. The pregnancy, labor and delivery were not unusual. Caudal anesthesia was employed.

As soon as the infant was delivered it was apparent that she was exceedingly weak and limp. The poor muscle tone and the generalized flaccidity gave her the appearance of a rag doll; the lower jaw sagged so much that her expression suggested that of a St. Bernard dog. She was unable to suck, and secretions of mucus formed a pool in the back of the pharynx. The weakness of the muscles of deglutition made one think of a patient with the bulbar type of poliomyelitis. It was not possible to induce gagging by the insertion of a tongue depressor in the pharynx. The eyelids were so weak that she could barely open her eyes. The tendon reflexes were active at both the knees and the ankles. There was very feeble movement of the extremities, even on stimulation by a pin. She seemed too weak to cry. Respiration and cardiac function were normal.

At times the baby nearly strangled on secretions that had collected in the pharynx and drained into the trachea. Suctioning of this fluid from this area quickly restored respiration to normal.

It was apparent that she could not take oral feedings, and therefore a polyethylene tube was introduced through a nostril and passed into the stomach. By this method the feedings were given at regular intervals.

Neostigmine was given by hypodermic injection, starting with 0.125 mg. every 4 hours. The dosage was gradually increased until 0.5 mg. was administered every 4 hours. There was definite improvement, as demonstrated by increased movements of arms and legs and by slight sucking movements of the lower jaw, but still she could not suck or swallow any liquid placed in her mouth.

This dosage of neostigmine resulted in moderate improvement in muscular activity, and yet it caused considerable amounts of secretions to form in the throat and bronchial tree. This caused alarming episodes of strangling and choking during which the baby became very cyanotic and seemed about to die. Aspirated secretions and formula caused areas of atelectasis and consolidation in the lungs. The use of atropine helped very little and proved actually more hazardous by producing thicker and more viscid secretions. Antibiotic drugs were given to help overcome the pulmonary infection.

At this point, when the patient was 10 days of age, a supply of pyridostigmine bromide was obtained and substituted for the neostigmine. From the time this change was made, she had no more episodes of strangling and showed a greater improvement in general muscle tone. The dosage was 1.0 mg. every 4 hours given by subcutaneous injection. (It is generally necessary to give 4 times as much pyridostigmine as neostigmine to get the desired cholinergic effect.)

To ascertain the optimal dose of pyridostigmine a daily test dose of edrophonium chloride (0.5 mg.) was given, and any increase in the patient's activity watched for. (This drug has effects similar to those of other cholinergic drugs, but it is of such short duration — 10 to 15 minutes — that it is relatively safe to use; if muscle strength is improved within a few minutes of administration of edrophonium, it can be concluded that the dosage of pyridostigmine was less than the optimal amount.) For a few minutes after the administration of edrophonium the patient sucked and smacked her lips; therefore, the dose of pyridostigmine was increased from day to day until 1.75 mg. was being given every 4 hours, subcutaneously.

At this point it was clearly apparent that the test dose of edrophonium was producing no increase in the patient's activity. Therefore, no further increase in the dose of pyridostigmine was made. If the optimal dose had been exceeded, the administration of edrophonium would have produced signs of overdosage — namely, fasciculation and greater muscle weakness — and might even have caused impairment of circulation and respiration. Atropine was kept at the bedside when these test doses were given.

Routine laboratory studies, including complete blood counts, urinalyses and spinal-fluid examination, and x-ray films of the chest revealed no significant or pertinent information. .

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†Kindly supplied as Mestinon by Robert J. Floody, M.D., of Hoffmann-La Roche, Incorporated, Nutley, New Jersey.

‡Available as Tensilon from Hoffmann-La Roche, Incorporated, Nutley, New Jersey.

The patient gradually improved in general strength and activity, and yet she could not suck well enough to take more than a few drops of formula. Improvement was so steady and so gradual that it was obvious that the pyridostigmine was not the chief factor in her progress; the passage of time was the really effective factor. By the time she was 3 weeks of age a reduction in the dosage of pyridostigmine was begun. As the patient grew stronger and approached a normal state of muscle activity the effect of the drug became less and less apparent. At 6 weeks of age it caused a response no different from that expected in a normal person, and therefore the drug was discontinued. For the next few days tube feedings were continued, and then she began to take the nipple. At the age of 16 weeks she was entirely normal in every respect, and weighed 6.4 kg. (14 pounds).

Discussion

To save the lives of these babies born with the more severe degrees of transitory myasthenia gravis it is essential that the condition be recognized by the physician responsible for their care. Otherwise, many of them will die, with an incorrect diagnosis of some cerebral defect.

Such a patient requires excellent nursing care and close medical observation, treatment being aimed at maintaining nutritional and fluid requirements; at the same time regurgitation and aspiration of fluids into the respiratory tract are watched for. These babies cannot prevent secretions from entering the trachea and in this respect resemble patients with bulbar poliomyelitis. The administration of neostigmine or pyridostigmine causes some increase in secretions of mucus, thus adding to the hazard of aspiration of fluids into the respiratory tract. Therefore, it is best to give the cholinergic drug in a dosage somewhat less than that producing maximum muscle strength, and thereby to achieve some diminution of the undesirable muscarinic side effects. It must be realized that a certain number of weeks (usually six or seven) must transpire before the infant can swallow normally, and the purpose of therapy is to keep the patient alive by the use of drugs aimed at moderate improvement of muscle strength; larger doses of the drug will not hasten the day when the patient is normal. The use of atropine to counteract the excessive secretions has proved unwise because the secretions become thicker and thus are more hazardous.

The use of pyridostigmine rather than neostigmine was very helpful in the treatment of this case because it produced less secretion of mucus. From the time pyridostigmine was substituted for neostigmine this patient suffered no more episodes of strangling on secretions. Before the drug was started, such episodes caused an alarming degree of cyanosis once or twice daily.

The use of edrophonium was very helpful in determining the proper dosage of pyridostigmine, affording a confidence that allowed the dose of pyridostigmine to be increased to the proper level — a procedure that would have been somewhat hazardous and alarming if done blindly.

The exact nature of the physiologic defect that causes myasthenia gravis is not completely understood. Investigations utilizing decamethonium salts (C-10) bring one closer to a comprehension of the abnormality. Zaimis[6] cites the convincing evidence presented by Churchill-Davidson and Richardson[7] that the neuromuscular block produced by decamethonium in normal human beings is due to long-lasting depolarization of the motor end plates, but the block produced by the same substance in myasthenia gravis is the result of a dual mode of action. Zaimis argues from these data that the myasthenic patient, like the monkey, represents a transition from the picture of a depolarizing block to that of a competitive block. This indicates that a change has occurred in the muscle membrane of the myasthenic patient, but the exact nature of this abnormality is still unknown. One can only speculate about what causes the muscle membrane of the newborn infant of a myasthenic patient to remain in a state of block for six to eight weeks.

Summary and Conclusions

A case of transitory myasthenia gravis in a newborn infant, demonstrating the urgency of correct diagnosis and prompt treatment, is reported. The use of pyridostigmine bromide (Mestinon) proved to be of great help because it produced fewer of the undesirable muscarinic side effects that were alarming while neostigmine was being given. Edrophonium chloride (Tensilon) helped determine the proper dose of pyridostigmine.

In the past, women with myasthenia gravis have been warned not to become pregnant. The use of these drugs so greatly facilitates the management of such an infant that women with myasthenia gravis can expect a greater chance of survival for their offspring.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

VIRGINIA W. TOWNE, *Assistant Editor*

BENJAMIN CASTLEMAN, M.D., *Editor*

CASE 41501

PRESENTATION OF CASE

A forty-year-old woman was admitted to the hospital because of coma of twenty-four hours' duration.

The history was obtained from an eighteen-year-old son, who was not very informative. In the recent past he had noted that his mother vomited rather frequently. A week before admission she became weak and went to bed. The weakness increased until she was unable to get up in the last few days. During the week before admission she ate practically nothing and vomited almost continually. A cough, which she had had for six months, became quite severe. On the day before admission she became disoriented and irrational and experienced visual hallucinations.

She had been in relatively good health until the present illness. She had never been observed to have jaundice, melena, hematemesis or tuberculosis. She was separated from her husband and had been living for the past two years with a man who had very recently died of tuberculosis. For many years she was a heavy wine drinker and poor eater.

Physical examination revealed an acutely ill, semicomatose, obese woman who was barely responsive to painful stimuli. The skin was very pale, dry and somewhat yellowish. No spider angiomas were seen. There were early decubitus ulcers on the back. The scleras were icteric; the fundi were normal. The breath had a foul odor, and the mouth was in poor condition. There was no nuchal rigidity. Both lung bases were dull to percussion. Coarse rales were audible diffusely, but were most prominent at the bases. The heart was not enlarged, but the cardiac sounds were obscured by the lung noises. The abdomen was protuberant. A fluid wave and flank dullness were present. There was some superficial venous distention on the abdomen. A firm, smooth liver edge was palpated 5 fingerbreadths below the right costal margin. The tip of the spleen was barely palpable below the left costal margin. The reflexes were normal.

The temperature was 103°F., the pulse 120, and the respirations 68. The blood pressure was 85 systolic, 40 diastolic.

Urinalysis was negative except for a + test for albumin. Examination of the blood revealed a hemoglobin of 6 gm. per 100 cc. and a white-cell count that ranged from 6200 to 10,000. One differential was 61 per cent neutrophils, 24 per cent large lymphocytes, 12 per cent small lymphocytes and 3 per cent basophils whereas a second showed 55 per cent neutrophils, 35 per cent band forms, 8 per cent lymphocytes and 1 per cent monocytes. The sodium was 124 to 125 milliequiv., the potassium 3.7 milliequiv., the chloride 73 to 75 milliequiv., and the carbon dioxide 21 milliequiv. per liter; the nonprotein nitrogen was 176 mg., the bilirubin 3.4 mg., the blood sugar 162 mg. (probably elevated because of an infusion of glucose), the phosphorus 10.5 mg., the alkaline phosphatase 4.1 units, the albumin 3.7 gm., and the globulin 4.21 gm. per 100 cc. The blood ammonia was 148 microgm. per 100 cc. The prothrombin time was 14 seconds (normal, 13 seconds). Cephalin flocculation was + + + in twenty-four and + + + + in forty-eight hours. Tests for barbiturate and bromide in the blood and a blood Hinton test were negative, as was a blood culture. Throat cultures grew abundant alpha-hemolytic streptococci, *Haemophilus influenzae*, *Neisseria catarrhalis* and diphtheroids, as well as a few pneumococci and rare coliform organisms. Acid-fast stains from a mucous plug in the pharynx were negative. A finger specimen of feces gave a negative

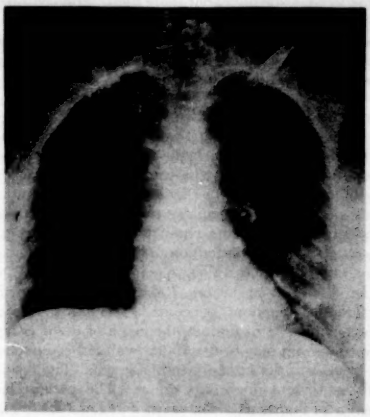

FIGURE 1. *Anteroposterior Roentgenogram of the Chest Taken with the Patient Supine, Showing an Ovoid Zone of Increased Density within the Lower Portion of the Left Lung.*

guaiac test. An electrocardiogram showed nonspecific T-wave and ST-segment changes, possibly as a result of left ventricular hypertrophy and strain. An x-ray film of the chest revealed a thin-walled cavity with a smooth inner border, 5.5 by 4 cm. in diameter, situated in the left-lower-lung field (Fig. 1).

There was very little consolidation in the surrounding lung. The patient was treated with blood, large amounts of fluids intravenously, antibiotics, including streptomycin and isoniazid, Cedilanid and Neo-Synephrine. Rehydration appeared to be successful, respirations improved, the blood pressure rose, and from time to time she appeared more alert. She continued to have a low output of urine, however, and the jaundice deepened. The temperature remained high until the fourth hospital day, when it dropped to between 98 and 99.5°F. and she died.

Differential Diagnosis

Dr. Perry Culver*: The paucity of historical information and particularly the abundance of obviously abnormal findings that can lead in various directions make it very possible for physicians to miss an important and perhaps remediable situation. This woman presented many of the characteristics of portal cirrhosis. If I give my attention to that primarily, I shall miss some other condition, I fear.

In discussing this case, I shall first consider the differential diagnosis of coma. There are hepatic coma, the coma of uremia, the coma of diabetes and the coma that may be associated with either infection or trauma to the central nervous system. The history tells us several important things. The patient had been a heavy drinker for years, and her food intake had been poor. Those facts make me suspicious that she had the background for nutritional or alcoholic cirrhosis. The persistent vomiting for the week or so before admission is unusual for an ordinary cirrhosis. If she was a spree type of drinker, she may have vomited after a bout of heavy drinking and then stopped drinking. It has been pointed out by various observers that the spree type of drinker as a rule does not acquire cirrhosis of the liver because the excessive alcohol intake during the spree is associated with little or no food intake; he then stops drinking and eats for a period, during which the liver has a chance to repair itself. Such drinkers may develop a Korsakoff type of picture. There is an adage postulated by Dr. Thomas C. Chalmers, at the Boston City Hospital, that "you have to eat to get cirrhosis." Obviously, if a patient eats well enough, he may not get it; but if he eats only enough so that he does not go into an acute alcoholic state, cirrhosis will develop. I suspect that this woman had been eating just enough to maintain her alcoholic intake at a fairly steady level.

Another important point is that while she was intoxicated she could have fallen and may not have recalled the episode. Her son may not have known that she had fallen. I think one has to worry about the possibility of subdural hematoma, which would explain some of the clinical picture. A subdural hematoma can produce neurologic changes, but it may be insidious in onset, with only drowsiness as the chief neurologic manifestation. I think we have to keep it in mind.

She must have had a very heavy exposure to tuberculosis so that one has to think of the possibility of tuberculosis involving the central nervous system and of course the lung to explain the cough and the x-ray findings in the chest. Such physical findings as the absence of nuchal rigidity, the normal reflexes and the normal fundi make me less concerned about the possibility of tuberculosis of the central nervous system.

On physical examination the picture of cirrhosis seems to be in evidence. The jaundice, the ascites, the enlarged liver and the enlarged spleen are all characteristic of cirrhosis. The splenic enlargement could possibly have been caused by tuberculosis, but that is rare. I could, I suppose, say that the patient had tuberculous peritonitis, but the picture was not characteristic of that. The lack of spider angiomas does not disturb me in the diagnosis of cirrhosis, although I should like to have seen spider angiomas to be on more sure ground. The obesity is not characteristic of a cirrhotic patient, whose arms and legs are wasted, but a woman who had lived on alcohol for a long time might be obese. Certainly, a number of patients with cirrhosis have been quite obese, without the typical wasting even though they had ascites. Perhaps she had not had ascites long enough for the wasted extremities to develop. The findings in the lungs suggest the possibility of fluid retention as the result of renal failure, congestive heart failure, which is probably unlikely, chronic pulmonary infection or tuberculosis or carcinoma of the lung. The roentgenograms of the chest may give us a clue about that.

The other findings on physical examination are simply those found in a woman who has neglected herself badly. The early decubitus ulcer suggests that she had been lying in bed a great deal and that her nutrition was not good. I am surprised that the serum albumin level was as good as it was. The foul odor of the mouth probably reflected poor dental hygiene. It is impossible to say whether this was fetor hepaticus or not.

The urinalysis was said to be negative. Among other things in this case there is apparently the problem of renal insufficiency. Was the specific gravity reported?

Dr. Benjamin Castleman: No; there was not enough urine obtained.

Dr. Culver: The absence of red cells in the urine is important. I wonder whether there were casts. I am thinking about a primary renal disease such as chronic glomerulonephritis, tuberculosis of the kidneys or even bile nephrosis. I do not know how long the jaundice had been present. The bilirubin level,

*Assistant physician, Massachusetts General Hospital.

however, was not very high so I should suspect that bile nephrosis probably had not occurred. Was there any specific report about the sediment?

DR. CASTLEMAN: No.

DR. CULVER: The white-cell count does not help me; it is consistent with any of the conditions I have mentioned, including tuberculosis and even chronic pulmonary infection, although with the latter, if there was much pulmonary sepsis, I should have expected a higher count. The hemoglobin of 6 gm. per 100 cc. has to be explained. There was one negative guaiac test on the stool. Were the red cells in the smear described?

DR. CASTLEMAN: There was marked variation in their size and shape and moderate hypochromia.

DR. CULVER: That description suggests an iron-deficiency type of anemia. I suppose that one can explain the anemia to a considerable extent on the fact that the patient had been chronically losing blood with the menstrual periods and was not replacing the iron sufficiently. One might wonder about the anemia of cirrhosis. The teaching is that cirrhotic patients have a macrocytic anemia. In the presence of iron deficiency, macrocytic anemia could not be demonstrated anyway. Whether or not there had been bone-marrow depression because of a chronic infection such as tuberculosis it is difficult to say. If this was a chronic tuberculous infection, amyloidosis may have been present and would explain the enlarged liver and spleen. There was no additional information to help me rule that in or out. I think that for the moment I shall say that she had an iron-deficiency anemia probably secondary to blood loss of menstruation and poor food intake.

The electrolytes in part reflect the vomiting and the marked dehydration. The only thing that disturbs me about them is the fact that the carbon dioxide was also low; I should have expected an alkalosis rather than an acidosis. Therefore, I wonder what was going on in the kidneys. The elevated nonprotein nitrogen may mean that there was a prerenal deviation of water because of the marked dehydration, but even when the patient was hydrated, the kidneys did not put out more urine. An elevated nonprotein nitrogen does occur in advanced cirrhosis, possibly because the liver may not inactivate the antidiuretic hormone and may thus promote a renal insufficiency. I cannot recall a nonprotein nitrogen quite this high in the terminal stages of cirrhosis. A nonprotein nitrogen of 70 to 90 mg. per 100 cc. would not be inconsistent but one of 176 mg. makes me suspect that there was a primary disease of the kidneys as well. Moreover, the elevated phosphorus suggests that there was marked impairment of renal function. The prothrombin time was normal. In cirrhosis there may be a considerable dissociation of disturbances in liver function, but in general with advanced liver disease, particularly in liver disease that has taken a patient into coma, one would expect a greatly impaired prothrombin time. The normal prothrombin time disturbs me because it does not ring true for an advanced alcoholic cirrhosis.

Ammonia intoxication has been of considerable interest as one of the possible explanations for hepatic coma. I think everybody who has been interested in hepatic coma is of the opinion that ammonia intoxication is certainly not the whole answer. The ammonia level of 148 microgm. per 100 cc. is considerably above the normal level of 40 to 70 microgm. Dr. William V. McDermott, Jr., tells me that he has seen the blood ammonia up to 100 microgm. or slightly more in uremia and renal disease. I suppose that one could again postulate that some of the increase in the blood ammonia level was the result of renal failure. On the other hand that level makes me suspicious that we are possibly dealing with hepatic coma.

The +++ cephalin flocculation is what one would expect with the alteration of globulin and albumin. The elevated globulin makes one think of fairly advanced liver disease. I suppose one could consider multiple myeloma as another cause of elevated globulin, but nothing else here helps to make that diagnosis. There was an albuminuria and an anemia, but the blood smear did not show plasma cells so that I shall pass multiple myeloma by.

The blood cultures and the throat cultures do not disturb me because we see these organisms over and over again in throat cultures done on our hospital employees. I should say from personal experience that this was a perfectly normal range of organisms. The fact that tubercle bacilli were not found is disturbing but not inconsistent with a diagnosis of tuberculosis.

May we see the x-ray films?

DR. JOHN D. REEVES: The examination of the chest is incomplete. We have only an anteroposterior film taken in the supine position on a comatose patient who was unable to stop breathing completely. In the left-lower-lung field there is a somewhat ill defined density (Fig. 1). The exact lobe in which this density lies cannot be predicted from this anteroposterior film alone. In the lower center of the density there is a slightly oval radiolucent area, the inner border of which, contrary to the protocol, is not smooth; its upper edge is somewhat ragged. If this is a cavity its oval shape is unusual. A film taken with the patient upright to demonstrate an air-fluid level would have been of help.

DR. CULVER: Do you see any sign of congestive heart failure?

DR. REEVES: No. There is slight prominence of the left ventricle; the pulmonary arteries are no larger than normal. An unexplained density at the left hilus could be a variation of the pulmonary artery. One cannot tell from this film alone.

DR. CULVER: Does this density suggest lymph nodes of the hilus of the left-lower-lung field?

DR. REEVES: Yes, it does, or it could be an anatomic variation in the pulmonary arteries. Fluoroscopy would be necessary to differentiate these.

DR. CULVER: In summary, this woman obviously had liver disease, probably portal cirrhosis with ascites, and a lung lesion that was either tuberculous or cancerous; she was in coma possibly from liver disease but probably from some other cause. I shall simply be guessing, but I should like to suggest that the coma was not the result of liver disease alone. I am going out on a limb and say that I suspect that she had a subdural hematoma, which explains the coma.

DR. CASTLEMAN: How did you account for the renal failure?

DR. CULVER: I have not been able to explain the renal failure except on the basis of the liver disease.

A PHYSICIAN: Did Dr. Culver consider the possibility of lung abscess in a person who was vomiting?

DR. CULVER: There are all sorts of possibilities, which I could not rule out. The exposure to tuberculosis made it one of the more obvious possibilities.

A PHYSICIAN: Do you believe that a lumbar puncture was indicated?

DR. CULVER: I wish that a lumbar puncture had been done and an electroencephalogram had been taken.

DR. JACOB LERMAN: What is the location of the cavity? Was it in the left lower lobe or in the lower part of the upper lobe?

DR. REEVES: It could be in either the lingula or the left lower lobe. I cannot tell from this view alone.

DR. LERMAN: Tuberculosis of the lower lobe is extremely rare without involvement of the remainder of the lung.

DR. ELBERT P. TUTTLE, JR.: About the renal disease, I gather from the concluding sentence that the patient was oliguric throughout the entire hospitalization.

DR. CULVER: I wondered if that was not secondary to the liver disease.

DR. TUTTLE: A twenty-four-hour urinary volume below 500 cc. would be against simple chronic nephritis, for the output with that condition is usually higher.

We have seen several cases of severe oliguria, less than 200 cc. of urine a day, associated with hepatic disease; 2 patients had acute cholangitis and stones in the common bile duct, 1 of whom also had multiple hepatic abscesses, and a third patient, discussed here in the clinicopathological conference, had a hepatoma that bled, leading to ligation of the right hepatic artery. One had some hematuria suggestive of ischemic necrosis, but the other 2 had no evidence of tubular necrosis in the sediment. None of the three was hypotensive. Their urines were not concentrated, and there was no evidence of obstruction either within the kidney or in the collecting system in 2 of them. Thus, it seems possible for oliguria, reduced glomerular filtration and azotemia to be associated with liver disease and not to be attributable to any of the usual causes of oliguria.

DR. CASTLEMAN: Dr. Ellis, what do you think the patient had?

DR. DANIEL S. ELLIS: I do not believe that she had a cerebral lesion such as a subdural hematoma. I should think that she had severe cirrhosis and an organic kidney lesion, perhaps the so-called hepatorenal syndrome. She died of a combination of hepatic failure, renal failure and the lesion in the chest, which may have been a lung abscess.

DR. WILLIAM V. MCDERMOTT, JR.: I should agree with Dr. Ellis. I do not think that the chemical studies relating to liver function provide enough evidence of liver disease for one to attribute the coma and death to a failing liver alone or to one of the hepatic comas. I do not like to refer to hepatic coma as a single entity.

DR. ELLIS: I think that there may be such chemical values with a fatal liver disease without associated renal disease if the disease is acute and fulminating.

DR. MCDERMOTT: Such as acute hepatitis?

DR. ELLIS: This case may have been an acute hepatitis superimposed on chronic renal disease.

DR. JOSEPH W. GARDELLA: I think a simple case of cirrhosis would be wasted on someone of Dr. Culver's acumen. I am attracted by the mass in the chest that does look like an abscess. I wonder if it underlies the diagnosis in this case.

DR. CULVER: It is possible. There have been a few cases of carcinoma of the lung with metastases to the liver, in which the lung lesion was not striking and the metastases to the liver looked like cirrhosis. I am not sure that I can make that diagnosis.

DR. CASTLEMAN: Dr. Decker, you saw this patient.

DR. BRIANT L. DECKER: I was on the Service when she came in. I am very pleased to see that everyone is as confused about the diagnosis as we were. We believed that she probably had a tuberculous cavity. She was receiving streptomycin and penicillin, and we added isoniazid as soon as we saw the film of the chest. We believed that she had cirrhosis on a nutritional basis and that she died of a combination of liver and kidney failure. We were disturbed by the fact that she was so oliguric. She was extremely dehydrated, — even more than the protocol suggests, — and after she had received a tremendous amount of fluid, she became temporarily more alert but she never did put out more urine. I believe that our best explanation for the oliguria was the effects of severe dehydration on the kidneys and the severe liver disease. Perhaps Dr. Keevil might give us more information about the opinion on the ward.

DR. C. S. KEEVIL, JR.: We were impressed by the oliguria. The patient did not put out more than 100 to 200 cc. of urine during the hospital stay. At one time we gave her a liter of 5 per cent dextrose in physiologic saline solution in an hour's time, with close checking of the vital signs. No increase in urinary output followed.

DR. TUTTLE: In the presence of hyponatremia with hypotension a salt load of this sort might be reasonable. I understand, however, that before coming to the ward she was given a test load of dextrose and water in an effort to increase the urinary output. This test has been used frequently in the past, especially in the treatment of oliguric patients suffering from severe burns, and I should like to comment on it. If a patient has a serum sodium concentration of 120 milliequiv. per liter, he has enough osmotically unobligated water to provide a water diuresis in the usual sense. Further dilution of the serum solutes will do nothing to suppress secretion of antidiuretic hormone. In addition there is the danger of water intoxication if the water load cannot be excreted. Hence, it is hard to imagine a situation in which a load of water without salt is indicated in a patient whose serum sodium is known to be below 125 milliequiv. per liter.

DR. CASTLEMAN: How long after the test did the patient die?

DR. KEEVIL: The test was done about 1 a.m.; she died at 7 a.m. two days later.

DR. CASTLEMAN: I am interested in that because there is something in the kidneys that interests me.

CLINICAL DIAGNOSES

Tuberculosis of lung.
Cirrhosis of liver, nutritional, with failure.
Kidney failure.

DR. PERRY CULVER'S DIAGNOSES

Pulmonary tuberculosis.
Cirrhosis of liver, nutritional.
Subdural hematoma.

ANATOMICAL DIAGNOSES

Miliary tuberculosis involving lungs, spleen, liver, peritoneum, intestines, bone marrow and pericardium.
Pulmonary tuberculosis with caseous pneumonia and cavitation, right upper lobe and left lower lobe.
Portal cirrhosis, alcoholic type, with severe fatty change and hepatomegaly.
Acute renal failure, ?lower-nephron nephrosis.
Splenomegaly.
Ascites.
Jaundice.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy the liver was cirrhotic, weighing almost 4000 gm. — a huge liver; microscopically, it showed the fatty and hyaline changes characteristic of the alcoholic type of cirrhosis. The spleen was enlarged to 640 gm. The lung cavity on the left side proved to be tuberculosis. Is this another cavity in the right lung, Dr. Reeves?

DR. REEVES: It could be.

DR. CASTLEMAN: That is where we found a cavity that measured 3 cm. in diameter.

DR. REEVES: One cannot be certain of too many changes in the lungs on one film of this type.

DR. CASTLEMAN: By the time she died there was also an extensive acute tuberculous pneumonia. Miliary tuberculosis had developed, with spread to many organs throughout the body, including the peritoneum in which there was half a liter of fluid, the pericardium, which contained fluid and tubercles over its surface, and the surface of the liver. The brain, however, did not give any evidence of tuberculosis. We made numerous sections and found no evidence of meningitis or other disease that could account for the coma.

Each kidney weighed 250 gm., which is about one and a half times the normal for a woman of 130 pounds. Microscopically, the striking feature was the considerable edema throughout the medulla. All the tubules were separated by a tremendous amount of fluid; in the normal kidney, the tubules are quite close to each other. In addition there was dilatation of the proximal tubules, and a great deal of proteinaceous material in the glomerular spaces and in the distal tubules. There were varying degrees of acute degeneration of the epithelial cells of both proximal and distal tubules. These findings are probably consistent with a lower-nephron nephrosis. In connection with this I should like to read from a paper by Oliver and his co-workers[1] in which they emphasize the importance of intertubular fluid:

> The leakage of tubule fluid into the interstitial tissue, a factor that might directly reduce the amount of fluid delivered to the collecting system, would seem to be one element in the production of the intertubular edema which may at times be so apparent in histological section. This edema in turn seems an important factor in the production of a rise in intrarenal pressure, a potential cause of oliguria by its pressure on tubules with a direct impedance of flow and on vessels, with an indirect effect in the same sense by its compression of thin afferent capillaries and a consequent exaggeration of renal ischemia and lessened filtration.

This case also raises the question of the so-called hepatorenal syndrome. In a recent series of papers More, professor of pathology at Queen's University in Canada, and his associates[2,3] have described changes in the kidneys of animals and man with liver disease that in some respects are similar to those in the case under discussion. They call the lesion "glomerulotubular nephrosis."

Whether these renal changes in the patient under discussion were in some way associated with the water-loading test or whether they were caused by the liver disease we cannot tell.

DR. CULVER: The water loading was not done until the patient was oliguric.

DR. CASTLEMAN: But it may have aggravated the pre-existing condition.

DR. CULVER: Many of the patients with cirrhosis who die have nonprotein nitrogen levels of 80 to 90

mg. per 100 cc. Did More see that in his patients?

DR. CASTLEMAN: Most of his patients did not have renal insufficiency.

DR. DECKER: In a case of cirrhosis with oliguria that I discussed at clinicopathological conference,[4] I thought that the renal condition that Dr. Castleman describes was present, but it was not reported pathologically.

DR. CASTLEMAN: I think the pathologist might easily miss such changes; he might not pay enough attention to fluid between tubules.

DR. DECKER: Were there tubercles in the kidneys?

DR. CASTLEMAN: There were very few.

DR. CULVER: Do you think that the miliary tuberculosis was present when the patient was admitted to the hospital?

DR. CASTLEMAN: I think so; she was in the hospital for only four days. How the renal failure and the liver failure developed is still a problem. More presents the hypothesis that a vasopressor factor that is ordinarily detoxified in the liver gets into the systemic circulation when the liver fails and acts on the kidneys to produce ischemia.

DR. TUTTLE: Do you think the changes are reversible? We have seen some patients who have recovered, and the oliguria has disappeared.

DR. CASTLEMAN: Yes.

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CASE 41502

PRESENTATION OF CASE

A fifty-five-year-old woman was admitted to the hospital because of a right inguinal mass.

Four days before admission the patient noted an asymptomatic right inguinal mass. One day later she experienced mild, crampy paraumbilical pain, which persisted. On the day before entry the right inguinal mass had doubled in size and had become hot, painful and tender. For two days before admission she was anorectic, did not eat and was mildly nauseated but did not vomit. Bowel movements were regular, and the stools were normal in color. Except for mild dysuria and urgency for one day four days before admission there were no urinary symptoms.

Bilateral varicose-vein ligation and stripping was done eight years previously. Incisions were made parallel to and 1 cm. below the groin creases bilaterally.

Physical examination showed an obese woman in no acute distress. There was diffuse lower abdominal tenderness and slight right-lower-quadrant spasm. A firm, hot, immovable, tender mass, 20 cm. by 10 cm., was palpated over the right inguinal ligament. The overlying skin was somewhat thin and reddened. The mass was not tympanitic on percussion, and no bowel sounds were heard over it. There were healed operative scars at the sites of the previous venous ligations. A healed phlebitic ulcer was noted over the right medial malleolus. Pelvic and rectal examinations were negative.

The temperature was 100.6°F., the pulse 102, and the respirations 20. The blood pressure was 135 systolic, 90 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.6 gm. per 100 cc. and a white-cell count of 18,600. The nonprotein nitrogen was 33 mg. per 100 cc. X-ray films of the abdomen were normal except for degenerative changes in the lumbar spine.

An operation was performed six hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. GRANT V. RODKEY*: May we see the x-ray films?

DR. C. C. WANG: The examination of the chest reveals a normal-sized heart and clear lung fields. There is no evidence of free air beneath the diaphragm. A film of the abdomen, which is grossly inadequate because of motion, gives no evidence of intestinal obstruction or unusual localized dilatation of the bowel. The psoas shadows on both sides are well seen. The kidney outlines are not unusual.

DR. RODKEY: I must confess that my imagination is limited concerning the conditions that might give this picture. The patient was a middle-aged, obese, acutely ill woman, who had the rapid appearance of a large tender mass in the right inguinal region that seemed to be external to the peritoneal cavity. In addition, there was evidence on radiologic and physical examination that there was no major disturbance within the abdomen itself — that is to say, there was no evidence of intestinal obstruction. Although she had tenderness and spasm in the right lower quadrant, the signs were not suggestive of peritonitis. One wonders whether the illness was related to the previous operation, but I do not see the relation. Bilateral saphenous-vein interruptions were done, and it might be postulated that a varix in the right femoral region had burst and formed a hematoma. However, that seems unlikely. It is hard to visualize any disease of the lymphatic system that would cause a mass of this size to develop so rapidly. I do not think that lymphadenopathy with abscess formation played a part in this picture. One might consider rupture of the bladder with extraperitoneal extravasation of urine, which

*Assistant in surgery, Massachusetts General Hospital.

may account for the appearance of a moderate-sized mass in a short time. The urine was normal, and it is quite unlikely that there would be no red cells or white cells in the urine in such a case. Furthermore, urinary symptoms were certainly minimal.

Suffice it to say that I come to the opinion that the patient must have had a hernia. Whether it was an inguinal or a femoral hernia I cannot decide, but the odds favor a femoral hernia since that is the more common location in women. If she had a hernia, the contents of the sac must explain the rapidly enlarging mass and the white-cell count that indicated impending gangrene or actual tissue necrosis — without intestinal obstruction or peritonitis. The bladder could have been incarcerated in such a hernia, but that is unlikely without signs in the urine. Rarely, an ovarian cyst may present through a hernial ring, but negative pelvic and rectal examinations should rule out this possibility. It seems more likely that the omentum was caught in the hernia and that the mass consisted of edematous omentum alone, or of omentum together with a knuckle of bowel — so-called Richter's hernia. In this condition the wall of the bowel is caught in the hernial ring, but there is no obstruction to the intestinal lumen. One cannot exclude that possibility in this case.

Of course, when people of this age present a hernia, one thinks of an associated malignant process. In this case, however, we have no history of previous bowel disturbances, negative rectal and pelvic examinations, normal hemoglobin level and no evidence in the plain film of the abdomen to suggest impending obstruction of the colon. There is no evidence to localize an associated carcinoma, and no real reason to suppose that one was present.

My diagnosis is inguinal or femoral hernia, incarcerated and strangulated, containing omentum and possibly a knuckle of small bowel — so-called Richter's hernia.

Dr. Marshall K. Bartlett: I was trying to think of what other structures might be implicated. Do you suppose a hydrocele of the canal of Nuck could behave in this way?

Dr. Rodkey: I cannot imagine why it would enlarge so quickly. A hydrocele is one of the anatomic structures to be considered, but unless the history is completely awry, this mass appeared in three or four days at the most. I do not know how a hydrocele could enlarge so rapidly.

Dr. Fletcher S. Colby: Could the patient have had an acute appendicitis within the hernia?

Dr. Rodkey: It is possible for the cecum to slip into such a hernia. Either large or small bowel may be incarcerated in a hernia of this region. If the cecum was incarcerated and necrotic, the appendix could be inflamed secondarily. I cannot find any reason for supposing that acute appendicitis was the fundamental disease.

A Physician: What do you think of the possibility of simply an abscess, a pyogenic abscess?

Dr. Rodkey: An abscess 20 by 10 cm. would not have developed so rapidly.

A Physician: Would you consider the possibility of a spontaneous rupture of the inferior epigastric artery, with resultant hematoma?

Dr. Rodkey: It is possible, but I do not think it likely. I thought of a number of conditions that might gravitate from the retroperitoneal area and present at the inguinal ligament. The patient may have had a hemorrhage — possibly even from a rupture of an aortic aneurysm — that presented as a hematoma in that region.

Clinical Diagnosis

Incarcerated femoral hernia.

Dr. Grant V. Rodkey's Diagnosis

Incarcerated and strangulated hernia, containing omentum and knuckle of small bowel.

Anatomical Diagnosis

Acute appendicitis within incarcerated femoral hernia.

Pathological Discussion

Dr. Benjamin Castleman: The surgeons also believed that this patient had an incarcerated femoral hernia. They did not indicate, however, what would be in the hernia. The operation was performed by Dr. Ditmore.

Dr. Harry B. Ditmore, Jr.: At operation the patient obviously had an incarcerated strangulated femoral hernia. When the sac was opened, we saw a knuckle of what at first appeared to be small bowel but on closer examination turned out to be the appendix itself. The knuckle of appendix was blackened and necrotic. The remainder of the appendix was inflamed, but not markedly so. This led me to believe that the course of events had been an initial strangulation and incarceration of a portion of the appendix, with secondary appendicitis.

Dr. Castleman: Was the tip of the appendix blackened?

Dr. Ditmore: The tip was not black and was probably viable. The midportion of the appendix, the knuckle that protruded into the hernia, was quite necrotic.

Dr. Castleman: The microscopical section of the appendix looked for the most part like that of an ordinary acute appendicitis, with necrosis of the epithelium in the lumen, but there were areas in the serosa that were very hemorrhagic, suggesting some degree of strangulation. At first I thought that this was merely an acute appendicitis, developing in the hernia, which led to strangulation. However, it may be that the appendix itself became strangulated first so that it was markedly congested and susceptible to infection and then acute appendicitis developed. Dr.

Bradley Coley, whom I asked to look up appendicitis in femoral hernial sacs, found a paper written in 1906 by Wood,[1] of the University of Pennsylvania, who had collected 100 similar hernias. Wood said that if the appendix alone was in the hernial sac the hernia was more often femoral than inguinal. In about 16 or 17 of his collected cases, the surgeon found a normal-appearing appendix at the time of exploration of the femoral hernia and returned it to the abdomen, with good results. In most cases the appendix was inflamed and adherent, and then the best treatment was to remove the appendix. The hernias that contained both the cecum and the appendix, according to Wood, were usually inguinal. Dr. Coley's grandfather[2] reported on a series of cases of hernia of the appendix in Keen's *Surgery*. He found that 2 per cent of hernias, both inguinal and femoral, contained the appendix.

DR. WILLIAM L. SWEET: May I ask Dr. Ditmore what else the sac contained? What made this mass so large?

DR. DITMORE: It contained a considerable amount of omentum; in addition there was a good deal of edema of the properitoneal fat and also of the fat of the thigh itself.

DR. CASTLEMAN: The mesoappendix was markedly swollen and hemorrhagic, as well as the piece of omentum that was removed with it. Where was the cecum, Dr. Ditmore?

DR. DITMORE: The cecum was rather low lying but in essentially the normal position. It was not within the hernial sac.

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9. Bookplate (apparently from a book at one time owned by Dr. John Warren) of Isaac Foster, a member of the Provincial Congress and the first surgeon engaged by the Council of War to care for the wounded after the battle of Lexington.

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ETIOLOGY OF SOME COMMON ACUTE RESPIRATORY DISEASES

IN the December 30, 1954, issue of the *Journal*, Huebner and his co-workers[1,2] presented papers dealing with a group of new cytopathogenic viruses obtained from cultures of human adenoid tissues. These agents were transmissible by serial passage in a variety of tissue-culture mediums, including those of HeLa cells and of certain human embryonic tissues. These viruses, which were designated "adenoidal-pharyngeal-conjunctival" agents, fell into 6 distinct groups, or types, of which Types 3 and 4 apparently were causes of specific pathologic entities. Type 4 appeared to be similar to the RI-67 virus isolated by Hilleman and Werner[3] from patients with some forms of acute respiratory disease and primary atypical pneumonia in military personnel. Type 3 was demonstrated to be the cause of an outbreak of febrile pharyngitis and conjunctivitis among children and adults at the new Clinical Center of the National Institutes of Health.

Type 3 has been isolated almost exclusively from nasopharyngeal or conjunctival secretions and anal excretions, the majority from persons with acute febrile pharyngitis and conjunctivitis. Types 1, 2, 5 and 6, on the other hand, were isolated almost exclusively from tissue cultures of human tonsils and adenoids, one or more of them being present in 57.4 per cent of children under fifteen years of age whose tissues were cultured.[4] They may still represent mostly "orphan viruses" in search of diseases with which they may be associated.

Hilleman and his co-workers,[5-7] by viral isolations and the demonstration of the development of specific antibodies, showed that the RI-67 virus was the cause of acute respiratory illnesses at Fort Leonard Wood, Missouri, during December, 1952, and early January, 1953, and among recruits at Fort Dix, New Jersey, in the winter of 1954. The frequency with which recruits acquired infection with the new virus varied markedly in different seasons. Antibodies were usually demonstrable by the second to the fourth week after onset of infection and declined gradually to low but detectable levels during the following year.

By antibody surveys these workers also showed that experience with this or related viruses was widespread in the general population, especially in middle life, but the significance of infections with these viruses is not yet clear. Like the workers at the National Institutes of Health, they noted that the new viruses formed a heterogeneous group when studied by serum neutralization tests, but they all seemed to have a complement-fixing antigen in common.

In view of these observations, Ginsberg and his associates[8] at Western Reserve University restudied serums obtained in 1945 from donors and recipients

of infected respiratory secretions during human transmission experiments. These studies indicated that the acute undifferentiated respiratory diseases with which they were concerned in 1945 were caused by an agent identical with or closely related to the RI-67 virus. They also showed that this acute respiratory disease was a clinical entity distinct from the common cold or primary atypical pneumonia, and believed that some cases were probably caused by other agents immunologically different from RI-67. However, 1 of their patients with "bronchitis simulating atypical pneumonia" showed a rise in titer of RI-67 antibodies. In further studies[9] they also isolated adenoidal-pharyngeal-conjunctival viruses from patients with nonbacterial pharyngitis among families in Cleveland during July and August, 1954; Type 3 was the predominant virus implicated, although at least 1 other immunologic type was shown to be associated with clinical cases.

From their studies the Cleveland workers considered it probable that the large group of acute respiratory diseases of unknown etiology will be reduced—perhaps only slightly, but significantly—and that certain acute respiratory infections that can be recognized clinically, identified etiologically and understood epidemiologically will then emerge. The etiologic agents of the 2 types of common cold with which the Commission on Acute Respiratory Diseases had been concerned, which probably embrace the majority of acute respiratory infections generally included under the designation of common cold, have yet to be isolated and identified.

Preliminary evidence has recently been presented that the adenoidal-pharyngeal-conjunctival viruses are also prevalent and cause infection in England. Eight strains of virus have been recovered from tissue cultures of human adenoids, and rises in titers of complement-fixing antibodies to some of these viruses were demonstrated in 20 persons with acute respiratory illnesses in Sheffield.[10]

Because of the demonstrated relation of the RI-67 and Type 4 adenoidal-pharyngeal-conjunctival viruses to the acute respiratory disease of recruits thoroughly studied at Fort Bragg during World War II and more recently in various military installations, Ginsberg and his co-workers[8] suggest that this type be called the acute-respiratory-disease virus. The workers at the National Institutes of Health, on the basis of the clinical, etiologic and epidemiologic features of the communicable disease that they studied and found to be caused by the Type 3 adenoidal-pharyngeal-conjunctival virus, proposed that the entity caused by viruses of this type be called "pharyngoconjunctival fever."[11]

The matter of nomenclature is rapidly getting out of hand, and it is hoped that agreement will soon be reached about the naming of the viruses and the various respiratory diseases with which they may be specifically linked.

A vaccine has already been produced from the Type 3 virus that gave promising results in preliminary experiments in volunteers.[12] However, the frequency of occurrence and the significance of this particular virus and of the disease that it produces are not yet clear. Nor will this vaccine, even if highly successful, be the solution of the problem of the "common cold," as generally recognized, although some lay reports have interpreted it as such.

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AMERICAN MEDICAL WRITERS' ASSOCIATION

The American Medical Writers' Association, recently affiliated with the American Association for the Advancement of Science, has made rapid growth in the fifteen years of its existence. This growth has been especially accelerated in the four years since its incorporation as a not-for-profit organization; its membership, in fact, with a total of nearly 700 on September 1, 1955, had increased by almost 200 during the year.

The purpose of such an organization as the American Medical Writers' Association—defined as "improvement of the written word of medicine"—represents a desire to meet a need much greater than is immediately apparent. This need is not only for an improvement in content of the thousands of medical journals in publication in the world. It is a need for the promotion of much better medical reporting in the lay press than is usually evident, for the assurance of factual and ethical advertising copy, and for the preparation of dignified and conservative material for the uses of pharmaceutical

houses and, in fact, for all such uses as they concern either the medical profession or the public.

The Association has accomplished much since its incorporation cleared the way for a more vigorous progression. In 1951 it added the publication of a quarterly bulletin to its activities. In 1952 it inaugurated a medical-manuscript-editing service,—probably the first such noncommercial service on the continent,—and in the same year it established honor awards for American and Canadian medical periodicals for distinguished service in medical journalism, and an annual distinguished-service award to be given an individual member "for distinguished contributions to medical literature or unusual and distinguished service to the medical profession." An honor award is also available to be bestowed from time to time on a nonmember of the Association who has made distinguished contributions to medical literature.

The most important recent result of the Association's activities has been the establishment of 3 four-year courses in medical journalism and writing, leading to a bachelor's degree, at the universities of Illinois, Missouri and Oklahoma. These courses, activated in September, 1954, are in their second full year of operation. A final development has been the establishment in 1954 of a visiting lectureship on medical writing, financed by a grant from Parke, Davis and Company. Under this lectureship, activated in March, 1955, Dr. J. P. Gray, director of Special Services of Parke, Davis and Company, has visited a number of teaching centers, where he has lectured to groups of medical students, interns, residents and faculty members.

Encouraging reports on these various enterprises were made at the twelfth annual meeting of the Association, held in St. Louis early in the fall. The 3 publications selected at that time for awards for distinguished service in medical journalism were *Public Health Reports,* published by the United States Public Health Service, for general medical periodicals with more than 3000 circulation; *A. M. A. Archives of Surgery,* for specialty periodicals; and the *Bulletin of Sangamon County Medical Society,* in Springfield, Illinois, for periodicals of county and city medical societies of less than 500 members.

"If I have at all learned the trade of using words to convey truth and to arouse emotion," Robert Louis Stevenson wrote in his "Letter on Father Damien," "you have at last furnished me with a subject." The American Medical Writers' Association can rest assured that it is playing some part in promoting the first of these uses.

PROGRESS AND PROBLEMS IN TUBERCULOSIS CONTROL

THE yearly Christmas Seal Campaign of the National Tuberculosis Association, which began on November 16 and will continue through December, serves as a reminder that a crippling and, at times, devastating disease, though curbed, has not yet been completely eradicated. The appeal for funds with which to continue the work of the Association and its 3000 affiliated organizations should be considered in terms of the fact that the forty-eight years since the first Christmas Seals went on sale represent the period of greatest advance in the control of tuberculosis.

The progress already achieved and the problems still to be solved bear a close relation to the immediate and ultimate aims of those concerned in the national effort to suppress the disease: education, case finding, rehabilitation and basic research in methods of control, treatment and prevention. Thus, whereas more and more people are recognizing the value of diagnosis, it is estimated that approximately 150,000 active cases are unreported to health authorities. The discovery of drugs effective singly and in combination has helped not only in the attack on the tubercle bacillus itself but also in control of infection during and after surgery on the lung—yet 400,000 patients have active, transmissible tuberculosis, and 800,000 have disease that, though arrested, may flare up and incapacitate them again. Finally, in spite of the remarkable advances made, approximately 100,000 new cases occur each year, and 17,000 patients die.

The work of the National Tuberculosis Association is a vital part of the national effort to change this still depressing picture. The large sums that must be raised in each yearly campaign are as nothing compared with the yearly cost of $620,000,000, largely in the form of tax-supported treatment and rehabilitation, or the incalculable cost of lives, working capacity and financial security. It is hoped that the sale of Christmas Seals this year will meet with a response as generous as the contributions made in previous campaigns.

RETIREMENT OF DR. BAILEY

ALL who know him personally or through his work will regret that Dr. Frederick J. Bailey has retired from the Boston Health Department after fifty-one years of service. A veteran in the field of public health, he has, through the years, won national recognition as an authority on infectious diseases. His activities as deputy health commissioner and chief of the Department of Communicable Diseases have contributed in no small measure to the splendid health record of the city of Boston for more than half a century.

The *Journal* joins Dr. Bailey's friends and associates in the good hope that he will continue to be active in public health and preventive medicine. Experience such as his can ill be spared by Boston and the Commonwealth at large.

Strange Hallucination.—*At a sale of the estate of the late Samuel Pointer, in Halifax County, the sum of $600 was paid for a* mad stone—*a mineral, supposed to have wonderful healing virtues.*—Richmond Whig.

Boston M. & S. J., *Dec. 20, 1855*

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Hypertension and Obesity, with Albuminuria

A forty-two-year-old gravida X, para IX, died in approximately the sixth month of pregnancy with the presumptive diagnosis of cerebrovascular accident. She had had extreme hypertension, enormous obesity and marked albuminuria.

The social and past obstetric history are of great importance. This patient lived in a 6-room house with 14 other members of the family. Her husband was unemployed and in debt. Three married daughters lived there with their unemployed husbands and their various children. One daughter and her illegitimate child also lived in this house. One of the patient's own children was a victim of cerebral palsy. The patient cooked and kept house for all these people.

Of the patient's known 9 preceding pregnancies 2 had involved stillbirth at thirty-two weeks. One of these fetuses was alleged to have weighed 5 kg. (11 pounds). High blood pressure and renal disease are known to have been present during at least the last 4 pregnancies, and with the eighth there had been severe post-partum hemorrhage.

Details of the immediately preceding pregnancy follow. At thirty-six weeks the patient had been transferred to the care of a maternity hospital after strong persuasion by the family doctor because her blood pressure was 274 systolic, 146 diastolic, and her weight 121.5 kg. (268 pounds). She had a ++++ test for albumin in the urine, marked dyspnea, cyanosis and pyelitis. Her legs were completely covered with a severe eczematous epidermophytosis. She was intensively treated and kept in the hospital, and delivery occurred about a month later. Attempts were later made at x-ray sterilization, but regular menstrual periods recurred in six months. Further efforts to reduce weight and blood pressure failed after about nine months, when she left the clinic.

Not seen for four and a half years, she returned to the maternity hospital again at the family physician's request approximately six months after her last period and now forty-two years old. She had felt quickening, had gained about 13.6 kg. (30 pounds) in weight and was complaining of extremely severe nausea, headache, edema and malaise. The blood pressure was 220 systolic, 130 diastolic, and the weight 117.9 kg. (260 pounds); the urine gave a ++ test for albumin. Pelvic and physical examinations were fruitless. X-ray examination for pregnancy was deferred because of obesity. A frog test was performed, and the patient told to return in two days for the report. She returned with a blood pressure of 300 systolic, 170 diastolic, an albumin of 750 mg., casts and bacteria. The frog test was reported negative. Therefore, the patient was considered not pregnant, being transferred immediately to a large general hospital, where she received a thorough examination, improving markedly during forty-eight hours. However, the diagnosis of pregnancy was still entertained. A plain film of the abdomen revealed a shadow consistent with fetal skull, and consultants thought that she was pregnant. Urine was taken for a Friedman rabbit test, and the patient was discharged on chlorpromazine for the nausea. She was instructed that a telephone report would be made to her regarding the results of the test and that, if she were pregnant, she should return at once to the maternity hospital. At this point the passage of time became a critical factor. The patient was admitted to the general hospital on a Monday and discharged on a Wednesday, forty-eight hours later. The rabbit was injected apparently on a Thursday morning, and the intern expected his report by Saturday morning, when he was to make his telephone call. For reasons that do not appear in the record, however, the laboratory report was not made until the following Tuesday morning, when the intern telephoned as planned. The person answering the telephone informed him that the patient had died the night before.

The family doctor later reported that she had suddenly been seized that evening with unilateral paralysis, cyanosis and dyspnea. Transferred to the local community hospital by ambulance, she died very shortly after admission. The medical examiner did not demand an autopsy.

The case was not classified for preventability. In view of the prior pregnancy and the serious condition that the patient had survived at that time, she might well have lived through this pregnancy also if appropriately treated. The severity of her underlying hypertensive and obesity states, however, made such an assumption unreasonable, and preventability therefore was not assigned.

However, in the opinion of the Committee there were two serious errors in management. The first was the failure of a maternity hospital to diagnose pregnancy. The unwarranted assumption that amenorrhea in a forty-two-year-old woman must be menopausal was matched only by the hope, five years earlier, that radiation, always a fallible method of sterilization, could possibly be effective in such a pa-

tient although one easily understands the reluctance for surgery. One gets the impression that the doctors threw up their hands in despair. Understandable as this is, it does not justify the failure to make x-ray examinations — a point that was proved in a clear demonstration of the fetus by those presumably less experienced elsewhere. But the greatest error is the reliance on a biologic test for pregnancy in the sixth month. All such tests depend on the presence of choriogonadotropic substances in the urine. It is well known that in this stage of pregnancy their level is often too low to affect the test animal. Arguments and statistics about the relative reliability of one animal over another are not germane, but criticism is justified on two counts: that the patient's fate was allowed to hinge upon *any* single test, particularly one of endocrine dimensions, and that the test was used at all at this stage of gestation.

The second serious error was made in the general hospital, which, after demonstrating the previously undiagnosed pregnancy with absolute and incontrovertible evidence, insisted on repeating the blunder of reliance on another — and needless — urine test. Apparently the intent was to prove a diagnosis doubly so that readmission to the maternity hospital could not possibly be refused. Unfortunately, this zeal for diagnosis was not matched by a zeal for treatment. It is apparent that those who discharged this woman did not recognize her precarious state, which should have been obvious to anyone remotely familiar with the hypertensive states in pregnancy. These are infinitely more dangerous than comparable blood-pressure and urine findings in the nonpregnant person.

JOHN FIGGIS JEWETT, M.D.
Chairman

REGARDING ACCREDITATION OF HOSPITALS

The following request is made by the American Medical Association Committee to Review the Functions of the Joint Commission on Accreditation of Hospitals:

In June, 1955, the House of Delegates of the American Medical Association authorized the Speaker to appoint a committee ". . . to review the functions of the Joint Commission on Accreditation of Hospitals . . ." and ". . . to make an independent study or survey and report its findings and recommendations to the House of Delegates at the next annual meeting. All physicians and hospitals are urged to pass on to this special committee any observations or suggestions concerning the functioning of the Joint Commission on Accreditation of Hospitals."

This committee was appointed, and now, in undertaking the task assigned to it, is seeking to obtain from physicians and others their observations concerning the functioning of the Joint Commission . . .

The Committee is interested especially in the following:

1. The general understanding by physicians of the functions of the Joint Commission.
2. Whether the method of appeal from an adverse ruling regarding accreditation is satisfactory.
3. The effect on the individual physician's hospital connections due to actions of the Joint Commission.
4. Whether any organizations not now represented should have official representation on the Joint Commission.
5. The effect of the Joint Commission's requirements concerning such matters as staff meetings.
6. The pros and cons of separating administrative and professional accreditation functions in the inspection of hospitals.
7. Constructive suggestions for improving the hospital accreditation program.

Any comments from individual members or state and county societies should be addressed to:

W. C. Stover, M.D., Chairman
Committee to Review Function of Joint Commission on Accreditation of Hospitals
535 North Dearborn Street
Chicago 10, Illinois

These comments should reach the Chairman not later than January 15, 1956.

W. C. Stover, M.D., Chairman, Boonville, Indiana
John F. Burton, M.D., Oklahoma City, Oklahoma
Gerald D. Dorman, M.D., New York, New York
George F. Gsell, M.D., Wichita, Kansas
Eugene F. Hoffman, M.D., Los Angeles, California
T. C. Terrell, M.D., Fort Worth, Texas
George Unfug, M.D., Pueblo, Colorado

ROBERT W. BUCK, M.D.
Secretary

DEATHS

GERRY — Frank Henry Gerry, M.D., of Arlington, died on October 25. He was in his sixty-third year.

Dr. Gerry received his degree from Middlesex University School of Medicine in 1920. He was a fellow of the American Medical Association and a member of the American Society of Anesthetists and the New England Society of Anesthetists.

He is survived by his widow and two sons.

PERKINS — Ralph S. Perkins, M.D., of Harwichport, died on October 2. He was in his seventy-first year.

Dr. Perkins received his degree from the Johns Hopkins University School of Medicine in 1911. He was a past president of the Worcester District Medical Society, a fellow of the American Medical Association and the American College of Surgeons and a member of the American Academy of Orthopedic Surgeons.

He is survived by his widow and two sons.

SMITH — John Jay Smith, M.D., of Cambridge, died on October 27. He was in his sixty-ninth year.

Dr. Smith received his degree from Howard University College of Medicine, Washington, D. C., in 1908. He was a fellow of the American Medical Association.

He is survived by his sister.

SOPHER — Curtis L. Sopher, M.D., of Wakefield, died on October 5. He was in his ninetieth year.

Dr. Sopher received his degree from University of Vermont College of Medicine in 1890. He was the first president of the newly formed Wakefield Medical Association in 1927.

BLUE CROSS–BLUE SHIELD

DIAGNOSTIC COVERAGE AND GENERAL PRACTICE

The Blue Cross–Blue Shield rider covering diagnostic services, which became effective on September 1, 1955, was written in such a way that general practitioners could be paid only for x-ray examinations

made in conjunction with acute traumatic conditions. At that time, it was not known how many general practitioners were equipped and qualified to do general x-ray work, and there was apprehension that, if the number was large, abuses might arise if physicians could indiscriminately refer patients to themselves for x-ray studies for other than traumatic conditions.

Since the rider was issued, a relatively small number of general practitioners have written letters of protest because of their exclusion. To evaluate the problem, the executive director of Blue Shield and an outstanding radiologist visited the offices of several of the physicians who had written in. On the basis of their findings the Blue Shield Board of Directors adopted the following recommendations of its Central Professional Service Committee, which were also approved by the Executive Committee of the Massachusetts Academy of General Practice:

1. No general practitioner who has purchased x-ray equipment since September 1, 1955, will be approved unless he can produce evidence of adequate formal training in radiology.
2. Any general practitioner who purchased his x-ray equipment prior to September 1, 1955, will be approved provided he has had a number of years of experience in x-ray and provided also that his equipment is adequate to carry out the examinations that he undertakes. This is in accordance with the accepted concept that through experience and study a general practitioner may become skilled in a given field. However, it should be clear that any physician would find it difficult, if not impossible, to qualify himself through experience if his equipment is inadequate.
3. In all instances the physician who interprets an x-ray film or who carries out a fluoroscopy must submit the Blue Shield Medical Service Report in his name regardless of who actually takes the x-rays. This is in accord with the concept that Blue Shield pays physicians primarily for their professional services and only secondarily for the maintenance of their offices. Furthermore, it lessens the likelihood of unethical practices which lead to poor medical care.
4. For x-ray examinations for other than acute traumatic conditions, the fee paid by Blue Shield and the fee paid by the member shall be computed in accordance with the Plan A Schedule of Fees whether the patient is a member of Plan A or a member of Plan B. This is in accord with the concept that a full time radiologist or a specialist fully equipped and qualified to make x-ray examinations within the confines of his own specialty has a higher unit cost than does a general practitioner. It also recognizes the limitation that radiologists may not refer patients to themselves and that the vast bulk of patients seen by specialists who make x-ray examinations within the confines of their own specialty are referred to them by other physicians.

CORRESPONDENCE

RABELAIS

To The Editor: Dr. Richard Warren's paper on Rabelais in the September 1 issue of the *Journal* contains the following sentence referring to certain books written by Rabelais: "Their dedication to influential people, such as that of the fourth book to Monseigneur Odet, Cardinal de Chatillon, and his ability to keep moving, saved him perhaps from the stake, where perished Servetus and Dolet, contemporaries of his who were hardly more unconventional than he." This sentence conveys the erroneous impression that Servetus, like Dolet, was burned at the stake after proceedings carried out under Catholic jurisdiction. Actually, Servetus met death in Protestant Geneva, where, "at Calvin's insistence, he was arraigned for blasphemy, condemned, and burnt to death" (*Encyclopaedia Britannica* Vol. 4, p. 632, 1954). Dolet, whose theological opinions were just as offensive to Calvin as they were to the Catholic authorities, was condemned and burned in Paris.

As for Rabelais, it is possible that even though stationary and devoid of influence, he would have been safe from the stake. Servetus and Dolet were burned not because they were "unconventional" but because they were heretical, which Rabelais probably was not.

MICHAEL V. MACKENZIE, M.D.
Malden, Massachusetts

PRESENT ORGANIZATION, PRODUCTS AND POLICIES OF THE LINCOLN FOUNDATION

To the Editor: Since the death of Robert E. Lincoln, M.D., on January 30, 1954, the Lincoln Foundation has been reorganized, and a new policy adopted for the guidance of its personnel and associates.

As present medical director of the Foundation, I have endeavored to establish cordial relations with the medical groups concerned, and to clear up previous misunderstandings. To this end, it is stated frankly that any and all law suits pending at the time of Dr. Lincoln's death have been withdrawn and annulled. Patent applications, previously filed, are not being pursued. The Foundation has no intention of maintaining secrecy or of withholding any essential information from those entitled to receive it.

Christopher Roos, who is director of laboratory research, was for many years senior bacteriologist of Sharp and Dohme Biological Laboratories and is fully experienced in biologic production and quality control. He has done considerable research on bacteriophages and has a keen interest in clinical bacteriology.

W. G. Workman, M.D., formerly chief, Laboratory of Biologics Control, National Microbiological Institute, National Institutes of Health, has given us invaluable aid and advice with the purpose of obtaining approval of laboratory procedure, standards and ultimate licensing of the bacteriophages for general distribution. He has stated, "I have complete confidence in Christopher Roos' ability to do the tests which are necessary to assure the safety and sterility of biologic products."

It is the main purpose of this memorandum to record the origin and identity of the bacteriophage as well as the staphylococcal strains used in the preparation of the lysates offered for clinical investigation.

The phage utilized by the Lincoln Foundation Laboratory is identified as Gratia B 985, obtained from a collection prepared and maintained by Dr. Edna Follensby, an associate of Dr. Sanford B. Hooker, of the Department of Bacteriology, Boston University School of Medicine. This particular strain was selected because of its marked polyvalency and high level of lytic activity.

For the propagation of this bacterial virus and for the preparation of the lysates, two strains of pathogenic *Staphylococcus aureus (Micrococcus pyogenes var. aureus)* were isolated by Dr. Follensby from specimens submitted by Dr. Lincoln; Lincoln Strain No. 1 (alpha) was taken from the nasal passages of a patient with acute sinusitis and infectious diarrhea, and Lincoln Strain No. 7 (beta) from a patient with acute sinusitis and infectious hepatitis. Both possess all the recognized characteristics of virulent toxigenic staphylococci. They are coagulase and phosphatase positive, ferment mannitol and produce alpha and beta hemolysins, exotoxins, enterotoxins, hyaluronidase, polysaccharides, fibrinolysin, protease, lipase and penicillinase.

These are cultured on mediums containing normal rabbit blood for the preservation of the specific properties desirable for lysate production. In preparation of the bacteriophages, the host cells are grown in tryptose beef-heart infusion broth —a medium proved to be nonsensitizing, both by guinea-pig and hamster tests and by clinical experience. The bacterial

viruses are added, and when lysis is complete, the solution is sterilized by filtration. A preservative is not used. The finished product has a high lytic activity, with a phage content of 10^{-9} to 10^{-10}. Animal sterility and safety tests are made according to the official methods and standards prescribed by the National Institutes of Health. The phages remain fully potent, under ordinary refrigeration, for at least three months.

The Department of Bacteriology at Boston University School of Medicine made and supplied all the lysates used and distributed by the Lincoln Foundation up to 1952. Since that time, routine production has been carried on regularly by experienced and competent personnel, under the supervision of Dr. Roos at the Lincoln Foundation Laboratory in Swarthmore, Pennsylvania.

The research programs of the Foundation envision the encouragement and promotion of laboratory and clinical investigation of staphylococcal bacteriophage — an agent long neglected and overshadowed by the vogue of sulfonamides and broad-spectrum antibiotics. Suggested lines of clinical research imply nothing covert, but do contemplate a fresh approach to clinical problems presented by foci of infection, antibiotic resistance, staphylococcal enterocolitis, and the appraisal of information that has accumulated. These are as follows:

Recognition of the nasopharynx and the skin as the principal reservoir of pathogenic staphylococci and the origin of many initial and secondary infections, reinfections, crossinfections and superinfections.

Emphasis on nasal aerosol administration of the phage lysates as a means of bringing them into direct contact with the upper respiratory mucosa, thus favoring rapid absorption and stimulation of the processes of active immunity by its potent vaccine action and local bacteriolysis.

The use of premedication or irrigation, or both, for the purpose of cleansing the mucous membranes and thus preparing a better absorptive surface.

Exploring the possibilities of staphylococcal bacteriophage lysates in the treatment of infections caused by antibiotic-resistant strains of micrococci.

Recognition of the significant synergistic action of staphylococcal toxins and spreading factors in allergies and infections due to these and other micro-organisms, and the feasibility of counteracting such effects with the bacteriophage.

Further study of the hyposensitizing value of the phage lysates in minimizing the bacterial allergenic factor in chronic sinusitis, bronchial asthma and many other chronic infections.

It is believed that these and related problems offer a broad and fertile field for clinical investigation.

A. Ernest Mills, M.D.
Medical Director
Lincoln Foundation
Medford, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Surgery of the Small and Large Intestine: A handbook of operative surgery. By Charles W. Mayo, M.D., Section of Surgery, Mayo Clinic, Rochester, Minnesota, and professor of surgery, Mayo Foundation, Graduate School, University of Minnesota. 8°, cloth, 340 pp., with 94 plates. Chicago: Year Book Publishers, Incorporated, 1955. $9.00.

The material in this handbook is divided into 4 sections. The first, dealing with diet, instruments and incisions, is followed by those on the small intestine, colon, rectum and anus and benign lesions. The publishing is good, and there is an index. The large number of full-page plates accounts for the high price.

Textbook of Biochemistry. By Edward Staunton West, Ph.D., professor of biochemistry, University of Oregon Medical School; and Wilbert R. Todd, Ph.D., professor of biochemistry, University of Oregon Medical School. Second edition. 8°, cloth, 1356 pp., with 140 tables and 84 illustrations. New York: Macmillan Company, 1955. $12.00.

In this edition a textbook first published in 1951 has been completely revised, and much material has been added. There is an extensive index, and the printing has been done on a light nonglare paper.

Genetica Medica: Ium symposium geneticae medicae. By Luigi Gedda. 8°, cloth, 467 pp., with illustrations and tables. Rome: Edizioni dell'istituto Gregorio Mendel, 1954. Prezzo L. 5.000.

This volume constitutes the proceedings of the first international congress on genetic medicine. Thirty papers were read and discussed. There are indexes of authors and subjects. The articles are written in the languages of the authors, but there are summaries in English, French, German and Italian. The volume is recommended for all collections on the subject.

Publicaciones del Centro de Investigaciones Tisiologicas. Vol. 17. Director, Prof. Roque A. Izzo. 4°, paper, 206 pp., with illustrations. Buenos Aires, Pabellon, Las Provincias, 1953.

This volume of an important series contains 20 articles on tuberculosis and related diseases. Lists of references are appended to the articles. The series should be in all collections on tuberculosis.

Casimir Funk: Pioneer in vitamins and hormones. By Benjamin Harrow. 8°, cloth, 209 pp., with 17 illustrations and a frontispiece. New York: Dodd, Mead and Company, 1955. $4.00.

NONCLINICAL NOTES

LIFE CHAIRMAN

Dr. Sidney Farber, professor of pathology at Harvard Medical School and pathologist to the New England Children's Medical Center, has been named life chairman of the United Cerebral Palsy Research Advisory Board. The appointment of Dr. Farber, which was announced at the sixth annual convention of United Cerebral Palsy, followed his presentation of the Max Weinstein Award for 1955 to Dr. Paul I. Yakovlev, clinical associate professor of neuropathology at Harvard Medical School.

STANLEY COBB FUND COMMITTEE

The Stanley Cobb Fund Committee of Harvard University announces that up to October 1, 1955, gifts have been received from 297 persons. These add up to a total of $270,009.41., and interest earned during the fiscal year 1954-1955 amounting to $6,153.10 has been added to the amount. At present the fund stands at $276,162.51.

VETERANS ADMINISTRATION ADVISORY COMMITTEE ON RESEARCH

The Veterans Administration announces the appointment of an advisory committee to counsel the Chief Medical Director concerning research programs within the Administration. The committee, composed of representatives of specialists in internal medicine, surgery, neuropsychiatry, and tuberculosis, is as follows: Dr. Joseph M. Hayman, dean of Tufts University School of Medicine, chairman; Dr. J. Burns Amberson, New York City; Dr. Carol A. Moyer, St. Louis; Dr. W. Reece Berryhill, Chapel Hill, North Carolina; and Dr. Harold Wolff, New York City.

NOTICES

ANNOUNCEMENTS

Dr. Albert M. Starr announces the opening of an office for the practice of neurologic surgery at 416 Marlboro Street, Boston 15, Massachusetts.

Dr. Robert J. Valin announces the opening of an office for the practice of neurologic surgery at 2279 Massachusetts Avenue, Cambridge 40, Massachusetts.

YALE UNIVERSITY SCHOOL OF MEDICINE YALE-NEW HAVEN MEDICAL CENTER

The program for "Lectures in the History of Surgery" for 1956, given by the Yale University School of Medicine, Yale-New Haven Medical Center, is as follows:

January 13. Harvey Lecture. The Development of the Residency System of Surgical Training. Historical Library. 8:15 p.m. Dr. Warfield M. Firor.

January 20. A Brief Review of the History of Neurologic Surgery. Beaumont Room. 5 p.m. Dr. Ernest Sachs.

January 27. History of Otolaryngology. Beaumont Room. 5 p.m. Dr. John A. Kirchner.

February 3. The Ancient Concepts of the Diagnosis and Treatment of Bladder Calculus. Beaumont Room. 5 p.m. Dr. Clyde L. Deming.

AMERICAN ACADEMY OF GENERAL PRACTICE

The eighth annual Scientific Assembly of the American Academy of General Practice will be held at the Armory, Washington, D.C., March 19-22, 1956.

During the four-day scientific meeting Surgeon General Leonard Scheele will present an address, and there will be two live clinics and a symposium on obstetrics. Special tours through the National Institutes of Health in Bethesda, Maryland, have been arranged.

The Academy's policy-making congress of delegates will convene in the Hotel Statler on Saturday, March 17, at 2 p.m. All sessions of the congress and many social functions will be held at the Hotel Statler.

SOCIETY OF NUCLEAR MEDICINE

The Society of Nuclear Medicine is receiving papers for presentation at its meeting at the Hotel Utah, Salt Lake City, Utah, June 21-23, 1956.

Titles and outlines of the proposed papers should be sent to Dr. Simeon Cantril, Tumour Institute, Swedish Hospital, Seattle, Washington. All papers should be submitted by January 1, 1956.

M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE

Cancer fellowships and residencies will be offered at M. D. Anderson Hospital and Tumor Institute under the auspices of the University of Texas Postgraduate School of Medicine. Participation in fundamental cancer research as well as a broad program of education in the Texas Medical Center will be offered in the following divisions: diagnostic radiology, therapeutic radiology, anatomic pathology, clinical pathology, experimental pathology, medicine, experimental medicine, surgery, experimental surgery, neoplastic diseases (rotating), anesthesiology, biochemistry, pediatrics, gynecology, physics and neurologic surgery. Further information may be obtained from Dr. Grant Taylor, Office of Education, University of Texas, M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25, Texas.

DAVID ANDERSON-BERRY PRIZE

A David Anderson-Berry silver-gilt medal and a money prize amounting to £100 will be awarded in 1956 by the Royal Society of Edinburgh to the person producing the best work on the therapeutic effects of x-rays on human diseases. Applications may be based on both published and unpublished work and should be accompanied by copies. All applications must be in the mail not later than March 31, 1956. Further information may be obtained from the General Secretary, Royal Society of Edinburgh, 22 George Street, Edinburgh 2, Scotland.

SOCIETY MEETINGS AND CONFERENCES

December 15. Arthritis Study Unit. Page 668, issue of October 13.
December 16. New England Roentgen Ray Society. Page 1048, issue of December 8.
December 16–28. Consultation Clinics for Crippled Children in Massachusetts. Page 937, issue of November 24.
December 20. Boston City Hospital House Officers' Association. Page 793, issue of November 3.
December 21. American College of Chest Physicians and Overholt Thoracic Clinic. Page 1048, issue of December 8.
January 9–14, 1956. Pan American Congress of Ophthalmology. Page 944, issue of November 24.
January 13, 20, 27 and February 3, 1956. Yale University School of Medicine, Yale-New Haven Medical Center. Notice above.
January 16, 1956. Hartford Medical Society. Page 708, issue of October 20.
January 16, February 6, March 5 and April 2, 1956. Fried Lecture Series. Page 535, issue of September 22.
January 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.
January 25, February 29, March 21 and April 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.
January 25, March 21 and April 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
January 30–February 8, March 19–28 and June 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
February 15, March 28 and April 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.
March 19–22, 1956. American Academy of General Practice. Notice above.
March 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.
May 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.
May 2–5, 1956. American Goiter Association. Page 348, issue of August 25.
May 28–June 1, 1956. European Symposium on Vitamin B. Page 578, issue of September 29.
June 21–23, 1956. Society of Nuclear Medicine. Notice above.
June 21–24, 1956. American Academy of Dental Medicine. Page 994, issue of December 1.
August 19–23, 1956. American College of Chest Physicians. Page 840, issue of November 10.

Calendar for the Week Beginning Thursday, December 22

Thursday, December 22
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Staff Conference. Dr. Howard B. Sprague. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

Friday, December 23
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Urological Conference. Auditorium, Carney Hospital, Dorchester.

(Concluded on page xxxv)